REDUCTION OF SERUM-CHOLESTEROL BY DEXTRO-THYROXINE IN MEN WITH CORONARY HEART-DISEASE

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A SUBSTANCE administered to reduce serum-cholesterol levels in patients with coronary heart-disease should not at the same time stimulate myocardial metabolism and increase myocardial oxygen requirements. Thus, lævo-thyroxine, which is a potent stimulant of basal and myocardial metabolism, is not suitable. Animal studies have suggested that the dextro-isomers of thyroxine, triiodothyronine and diiodothyronine produce less myocardial stimulation than the corresponding lævo-isomers but retain the ability to reduce elevated serum-cholesterol levels (Boyd and Oliver 1960a, Cuthbertson et al. 1960). This suggestion has to some extent been confirmed by clinical studies (Boyd and Oliver 1960b) although these dextro-isomers also stimulate myocardial metabolism and lead to angina if given at a dose only slightly in excess of that required to reduce serum-cholesterol. These dextro-isomers lower serum-cholesterol levels for periods up to three months whereas certain lævo-isomers and acetic-acid analogues do not have such a prolonged effect (Oliver and Boyd 1957, 1959). The difference between the dose required to lower serum-cholesterol and the dose which produces angina is greater for dextra-thyroxine than for the other two dextro-isomers and it was felt, therefore, that dextro-thyroxine required further clinical assessment.

Methods

The subjects were 38 euthyroid men between the ages of 35 and 53 with electrocardiographic evidence of myocardial infarction or myocardial ischæmia after exercise. None had sustained a myocardial infarct during the four months preceding administration of dextro-thyroxine. All were outpatients engaged in regular employment and no changes were made in their usual activities or dietetic habits.

TABLE I—EFFECT OF 10 mg. DAILY OF DEXTRO-THYROXINE (DT4) ON SERUM-CHOLESTEROL (mg. per 100 ml.) OF 12 HYPERCHOLESTEROLÆMIC EUTHYROID MEN WITH CORONARY HEART-DISEASE

Case	12 wk. before DT4	4 wk. before DT4	Day before DT4	DT4 administration 4 weeks	DT4 administration 8 weeks	DT4 administration 12 weeks	2 wk. after DT4	4 wk. after DT4	6 wk. after DT4
1	310	273	309	229	226	218	346	302	304
2	284	268	284	223	222	219	245	333	298
3	271	266	272	204	202	210	250	267	264
4	330	330	312	219	205	201	299	355	324
5	311	326	302	265	281	319	312	296	304
6	284	286	268	204	214	209	300	316	290
7	262	270	274	216	221	208	281	268	262
8	274	278	275	216	226	224	279	266	254
9	277	281	271	224	218	222	288	317	306
10	268	272	275	244	273	286	272	250	260
11	301	335	304	206	224	210	310	354	301
12	264	290	288	225	236	217	288	317	306
Mean of 12 men	286	290	286	223	229	229	289	303	289

Serum-cholesterol was estimated by the Sperry and Webb modification (1950) of the Sperry-Schoenheimer procedure; protein-bound iodine by the chloric-acid digestion procedure of Zak et al. (1952), using Grossmann and Grossmann's (1955) brucine modification of the Chaney (1940) ceric-sulphate technique; and the uptake of radioactive iodine by obtaining the neck-thigh ratio four hours after the oral administration of 20 microcuries of ^{131}I. Details of the design of the investigation have recently been published (Boyd and Oliver 1960b).

The dextro-thyroxine administered in these studies was identical with that previously assayed in rats (Boyd and Oliver 1960a); it is free from contamination by tetraiodothyroacetic acid and the possible contamination by lævo-thyroxine was less than 3%.

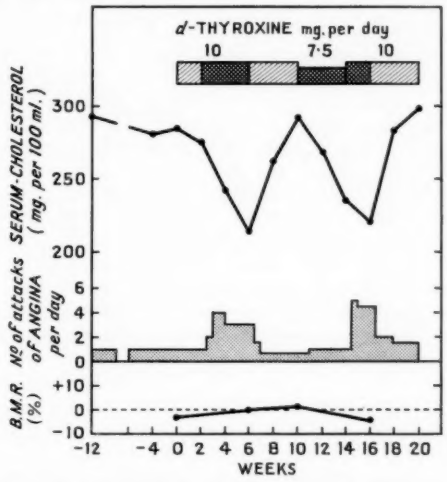

Fig. 1—Effect of 10 mg. daily and of 7·5 mg. daily of dextro-thyroxine (DT4) and of inert tablets on serum-cholesterol levels and incidence of angina in 2 men with coronary heart-disease. (Hatched blocks indicate when inert tablets were administered.)

Results

10 mg. Dose

To 12 hypercholesterolæmic men with coronary heart-disease, 10 mg. of sodium dextro-thyroxine was given daily for twelve weeks (table I). The mean serum-cholesterol was reduced by 20%, although in 2 patients (cases 5 and 10) there was no sustained fall. There was no significant increase in the basal metabolic-rate and no sign of increased thyroid activity but there was a mean weight-loss of 4 lb. There was no increase in the incidence or severity of effort angina and there were no consistent or significant electrocardiographic changes.

Subsequently, a comparative study was made of the effect of the daily administration of 10 mg. of the sodium salt with 10 mg. of the free acid of dextro-thyroxine to a further 6 hypercholesterolæmic men with coronary disease. No difference was observed in the potency of the sodium salt and free acid in respect of the effect of reducing serum-cholesterol levels. Angina developed in 2 of the 6 men and, after the completion of this comparative study, 10 mg. of dextro-thyroxine was again administered daily to these 2 men. Angina recurred with both preparations but disappeared when inert tablets

or 7·5 mg. of either dextro-thyroxine were administered (fig. 1). Potentiation of angina has previously been reported with larger daily doses of dextro-thyroxine (Boyd and Oliver 1960b), and the development of angina in 2 of 18 euthyroid men when given 10 mg. daily indicated that the effects of a smaller daily dose required study.

7·5 mg. Dose

To 20 euthyroid men with coronary heart-disease, 7·5 mg. of dextro-thyroxine (free acid) was given daily for six months (table II and fig. 2). Only 9 of these 20 men had hypercholesterolæmia (serum levels greater than 270 mg. per 100 ml., Oliver 1958). In case 1 there was no significant change in serum-cholesterol levels; in addition to myocardial infarction, this man had tuberous xanthomatosis and it has been our previous experience that the serum-cholesterol of such patients does not commonly respond in the expected manner. In 5 patients (cases 2, 9, 10, 14, and 16), the serum-cholesterol level was lowered significantly during the first few months but this reduction was not maintained throughout the six months' administration of dextro-thyroxine; the protein-bound iodine levels of these 5 men remained high during these six months and there is no evidence to indicate that they did not take the dose of dextro-thyroxine. The mean serum-cholesterol level of 19 men (excluding case 1) fell by 26% after two months but was only 16% lower than the pre-treatment value after six months of dextro-thryoxine administration; moreover, 3 patients (cases 5, 12, and 13) showed no consistent reduction of serum-cholesterol. The mean serum-protein-bound iodine rose from a pre-treatment level of 6 μg. per 100 ml. to a maximum of 17 μg. per 100 ml., and its elevation was regarded as a useful index that the patients were taking dextro-thyroxine conscientiously. The 4-hour uptake of radioactive iodine fell from a pre-treatment level of 16% to 2%, but in no patient was there any feature to suggest hypothyroidism. There was no significant change in the mean basal metabolic-rate, although 1 man developed a fine tremor of his hands and an increased tendency to sweat and another complained of sleeplessness. There was a mean fall in weight of 4 lb. 1 of the 20 patients developed an increase in the incidence and severity of his pre-existing angina. This study was made between

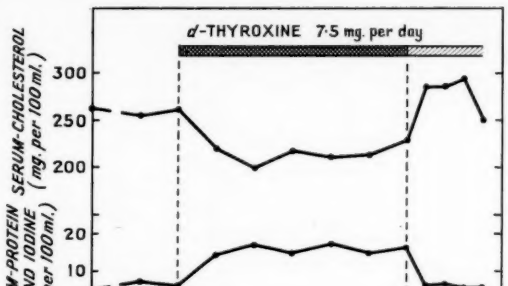

Fig. 2—Effect of 7·5 mg. daily of dextro-thyroxine (DT4) on serum-cholesterol, protein-bound iodine, radioactive-iodine uptake and basal metabolic-rate in 20 euthyroid men with coronary heart-disease. (Hatched block indicates when inert tablets were administered.)

the months of April and October and thus extremes of climatic temperature variations were avoided.

After the withdrawal of dextro-thyroxine and substitution of identical inert tablets, there was an abrupt rise in serum-cholesterol levels, a fall in serum-protein-bound iodine, and a rise in the 4-hour uptake of radioactive iodine (fig. 2). There was a mean increase in weight of 5 lb. over a period of four weeks. During the six weeks of observation following the withdrawal of dextro-thyroxine, 7 of the 20 men spontaneously commented that the incidence and severity of angina had decreased and that their effort tolerance was improved; none of these men, on close questioning, would admit that angina had become more frequent or that their effort tolerance had been reduced while they were taking dextro-thyroxine. There were no consistent or significant electrocardiographic changes.

TABLE II—EFFECT OF 7·5 mg. DAILY OF DEXTRO-THYROXINE (DT4) ON SERUM-CHOLESTEROL (mg. per 100 ml.) OF 20 EUTHYROID MEN WITH CORONARY HEART-DISEASE

Case	12 wk. before DT4	4 wk. before DT4	Day before DT4	DT4 administration						2 wk. after DT4	4 wk. after DT4	6 wk. after DT4	8 wk. after DT4
				4 weeks	8 weeks	12 weeks	16 weeks	20 weeks	24 weeks				
1	424	369	386	394	426	425	366	366	510	517	615	654	482
2	242	246	249	201	175	155	168	198	235	250	238	247	249
3	236	252	260	218	211	155	216	185	218	276	286	301	253
4	215	244	229	189	192	188	204	226	183	223	254	271	243
5	257	239	252	218	210	226	236	218	232	271	291	336	262
6	248	237	246	190	200	206	217	190	192	288	252	260	231
7	276	300	282	241	214	245	257	256	266	319	348	314	276
8	214	193	204	159	139	159	150	140	145	216	209	210	194
9	219	208	182	185	140	182	177	180	220	232	250	234	201
10	235	223	257	204	212	217	185	196	246	294	268	300	218
11	285	260	284	245	177	209	204	213	210	270	270	281	262
12	194	220	191	177	147	236	185	193	161	247	228	240	207
13	299	266	272	250	226	256	279	281	234	315	286	309	254
14	274	270	273	227	224	213	224	226	256	333	279	305	236
15	263	276	290	231	216	210	205	227	215	291	298	281	262
16	276	284	281	196	146	210	206	210	234	246	258	262	218
17	264	252	266	245	209	206	201	216	229	301	266	291	256
18	208	212	210	171	135	186	131	149	166	224	230	240	193
19	296	260	284	209	138	195	166	156	165	239	244	197	221
20	279	270	281	240	209	245	232	216	220	313	319	315	267
Mean of 20 men	260	254	258	219	197	216	210	212	227	283	284	292	249
Mean excl. no. 1	252	248	252	210	185	205	202	204	212	271	267	273	237

Discussion

This clinical assessment of the administration of dextro-thyroxine to euthyroid men with coronary disease indicates that a daily dose of 7·5 mg. will, in the majority, reduce the serum-cholesterol level without producing angina. Yet the response was variable and in 4 men there was no consistent reduction of serum-cholesterol and in 5 other men the serum-cholesterol levels were higher after six months than during the first few months. This observation indicates that prolonged administration of dextro-thyroxine does not result in continued depression of serum-cholesterol in all individuals. Of 18 men given 10 mg. of dextro-thyroxine daily, 2 developed effort angina. Although only 1 man observed an increase in angina while receiving 7·5 mg. of dextro-thyroxine daily, 7 experienced less angina and considerable improvement in effort tolerance during the six weeks after withdrawal of dextro-thyroxine and substitution of identical inert tablets. There would seem to be two possible explanations for this. One is that the administration of dextro-thyroxine did, in fact, reduce effort tolerance but the effect was so gradual and insidious that it was not noticed. Another is that, following the withdrawal of dextro-thyroxine, these men became temporarily hypothyroid until their thyroid tissue started once more to produce the physiological thyroid hormone. This possibility is supported, to some extent, by the high serum-cholesterol levels and the abrupt rise in weight after the withdrawal of dextro-thyroxine.

The rise in protein-bound iodine during the administration of dextro-thyroxine can be accounted for by the comparatively large amounts of iodothyronine administered. Decrease in the radioactive iodine uptake by the thyroid has been observed previously (Starr and Leibhold-Schueck 1953) and regarded by Greene and Farran (1958) as due to decreased production of thyroid-stimulating hormone. While this effect of certain thyroxine analogues may be due to a thyroxine-like action of the analogue (Slater et al. 1960), Alexander et al. (1961) concluded from stable iodide studies that the absolute iodine uptake by the thyroid in microgrammes per hour is increased rather than decreased. They suggest that the decrease in radioactive iodine uptake results from an increase in the extrathyroidal iodine pool arising from the inorganic iodine liberated by the breakdown of dextro-thyroxine in the tissues.

The difference in the relative effect on the serum-cholesterol levels and myocardial metabolism between lævo- and dextro-thyroxine has not yet been satisfactorily explained in man, although Tapley et al. (1959) have indicated that the physiological distribution of these two isomers in the tissues of the normal rat is sufficiently different to explain any difference in activity between these isomers. Moreover, these workers have shown that the oxygen consumption of rat heart is less in animals injected with dextro-thyroxine than in those injected with an identical quantity of lævo-thyroxine (Dunne and Tapley 1960).

Most of the reported studies of the administration of dextro-thyroxine have been made on hypothyroid patients or euthyroid patients without coronary heart-disease (see Starr et al. 1960). In general, the dose of iodothyronines necessary to reduce serum-cholesterol in hypothyroid patients is approximately one-third of that required to produce the same metabolic effects in euthyroid patients (Boyd and Oliver 1960b), and studies of the administration of dextro-thyroxine to hypothyroid patients have been concerned with doses between 2 and 4 mg. daily. There have been few studies of the effects of dextro-thyroxine administration to euthyroid patients with coronary heart-disease. It has been reported that 4 mg. daily is insufficient to produce significant depression of the serum-cholesterol levels in all patients (Hoobler et al. 1959) and that 8 mg. daily cannot always be relied on to maintain continued depression of serum-cholesterol even after six months' adminstration (Jones 1960). In the latter study, 8 mg. daily produced angina in 3 of 14 euthyroid patients with coronary heart-disease and an increased incidence of angina has also been reported with 6 mg. daily (Goldstein 1960).

These investigations, and the larger study here reported, indicate that dextro-thyroxine is a moderately efficient substance for reducing serum-cholesterol but not sufficiently reliable for widespread administration to patients with coronary heart-disease. Yet earlier studies have indicated that it is probably the most satisfactory thyroactive compound presently available for this purpose. Thus, it seems that at present there is no thyroactive substance which has sufficiently complete dissociation of the metabolic and myocardial stimulant action from the cholesterol depressant action for safe and continued administration to patients with coronary heart-disease.

Summary

Dextro-thyroxine has been administered for periods of three to six months to 38 euthyroid men with coronary heart-disease for the purpose of reducing the levels of serum-cholesterol. This purpose was achieved in the majority of men.

Of 18 men, to whom a daily dose of 10 mg. was given for three months, 2 showed no significant or sustained reduction of serum-cholesterol levels and 2 others developed effort angina.

Of 20 men, to whom a daily dose of 7·5 mg. was given for six months, 4 showed either no fall or no consistent reduction in serum-cholesterol levels. Dextro-thyroxine produced significant reduction of the serum-cholesterol in the remaining 16 men, but in 5 of these 16 the serum-cholesterol rose after six months to levels higher than at any other time during dextro-thyroxine administration. Elevation of protein-bound iodine and marked reduction of he four-hour uptake of radioactive iodine occurred in all. Of these 20 men, 1 developed effort angina and complained of reduced effort tolerance and 7 other men experienced less angina and improvement in their exercise tolerance after withdrawal of dextro-thyroxine. This effect is discussed.

Although our previous investigations have indicated that dextro-thyroxine is at present the most satisfactory thyroactive compound for reduction of hypercholesterolæmia in patients with coronary heart-disease, it is not good enough. The variation in individual response is striking and such that there is no dose which can always be relied on to reduce the level of serum-cholesterol over a period of six months. Nor is there a dose which will be certain to reduce the serum-cholesterol without occasionally provoking angina.

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References overleaf

CHROMOSOME COMPLEMENT IN A CASE OF THE "MALE TURNER SYNDROME"

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IN 1938 Turner [33] described a triad of infantilism, webbing of the skin of the neck, and cubitus valgus, in seven girls aged 15 to 23 years. Published in the journal *Endocrinology*, Turner's syndrome became known as an endocrine disorder of small girls with amenorrhœa and absence of secondary sex characteristics. Such girls, whose sexual infantilism becomes a medical problem as a rule after the age of adolescence, had been described before Turner by Funke (1902) [13] and Baer (1927).[1] In 1930 Ullrich [35] reported the case of a preadolescent girl born with œdematous swellings on the hands and feet, pterygium colli, ptosis of the upper eyelids, high arched palate, low-set ears, low hair-line of the neck, small nipples, cubitus valgus, umbilical hernia, and irregularities of the nails. The internal organs appeared normal. The endocrine manifestations of the syndrome understandably escaped Ullrich, who was dealing with a girl only 8 years old. The syndrome he described [35] in a pædiatric journal became known in the pædiatric literature as a disease picture of "congenital multiple degenerations". This syndrome of congenital malformations in which lymphangiectatic œdema played a leading part was extended to a variety of teratological disease pictures, including asymmetrical defects of the cranial nerves, pectoralis muscle, and hand, and was explained by "myelencephalic blebs".[36] Submerged in the "status Bonnevie-Ullrich", which was applied chiefly to asymmetrical anomalies on or near the body surface, the symmetrical cases of congenital lymphangiectatic œdema showing external as well as internal malformations were only slowly recognised as the childhood form of Turner's syndrome. It is now possible to diagnose Turner's syndrome—or the "symmetrical form of the status Bonnevie-Ullrich"—with a high degree of probability at birth, when pterygium colli, lymphangiectatic œdema of hands and feet, deformities of the ears, ogival palate, hypoplasia of the nipples, and dystrophy of the nails foreshadow the lack of growth and sexual development in later life.

Subsequently, it was established that girls with Turner's syndrome often have a high output of urinary gonadotrophins,[23 37] gonadal agenesis,[38] negative sex-chromatin,[25 39] and a chromosomal XO karyotype.[8 11 20 32] Apart from the anomalies of sexual constitution and development, additional congenital malformations were seen in patients with Turner's syndrome. Hypertelorism, epicanthic folds, micrognathia, long and narrow auricles, congenital heart-disease, renal malformations, shortening of the metacarpal, metatarsal, or phalangeal bones, and many other deformities have been described. Consequently, in addition to the endocrine disorder, a teratological syndrome emerged. Later, it was found that persons showing the syndrome of congenital malformations usually associated with Turner's syndrome need not have amenorrhœa and absence of secondary sex characteristics,[24] and that about 20% of the patients with Turner's syndrome have a positive sex-chromatin pattern.[15] On the other hand, it became known that many of the congenital malformations and anomalies characteristic of Turner's syndrome can occur in phenotypical males.[5–7 14 21 22 26 27 29–31 34] Three children of this type have been seen in the pædiatric department of the University of Cincinnati: in one of them analysis of the chromosomal complement could be performed.

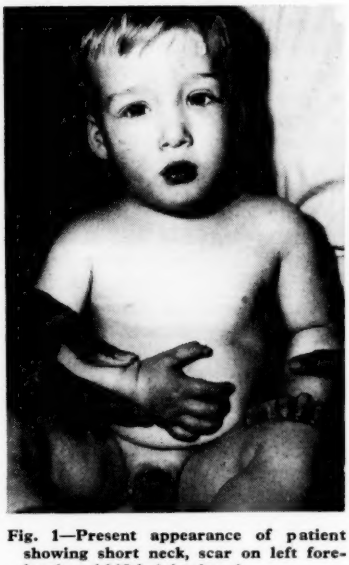

Fig. 1—Present appearance of patient showing short neck, scar on left forehead, and bifid right thumb.

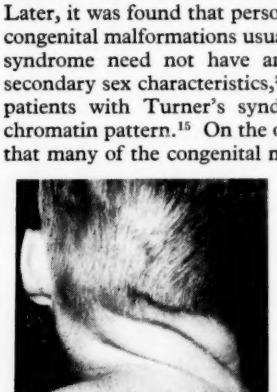

Fig. 2—Loose skin fold of the neck.

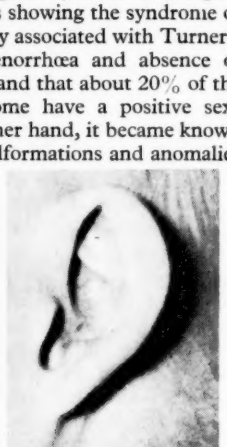

Fig. 3—An ear showing the broad helix forming a gothic arch, small triangular fossa of the auricle, and the absence of lobule.

Case-report

This patient, born on June 13, 1958, was the son of a 29-year-old woman, the result of her first pregnancy. Family history

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obtained was neither satisfactory nor reliable. The pregnancy had been uneventful and no drugs were used before the child's birth. Gestation lasted 38 weeks and the birth-weight was 2580 g. (5 lb. 11 oz.). Labour and delivery were uneventful.

The baby had a short neck, a scar on the left forehead (fig. 1), and swollen dorsa of the hands and feet. The right thumb was bifid, and he had a heart murmur. X-rays of the cervical spine showed normal development of the vertebræ.

The patient was admitted to the Cincinnati Children's Hospital for the first time at the age of 4 months because of congestive heart-failure, cyanosis, and left lower-lobe pneumonia. He was treated with digitalis and penicillin, and responded to this therapy. The tentative clinical impression was pseudotruncus arteriosus. Because of the loose skin folds of the neck (fig. 2), the shape of the auricles (fig. 3), the congenital lymphangiectatic œdema of the hands and feet (fig. 4), the bifid thumb, and congenital heart-disease, the diagnosis of "Bonnevie-Ullrich" or "male Turner syndrome" was entertained.

Fig. 4—Congenital lymphangiectatic œdema of feet.

He was again admitted at the age of 18 months with a respiratory infection and congestive heart-failure. This time he responded to penicillin and oxygen therapy, and was discharged after 2 days in the hospital. A buccal smear for sex-chromatin was read as being chromatin-negative.

The child was again readmitted at the age of 21 months for cardiac catheterisation and amputation of the small excrescence of his thumb. He had been able to sit up at 6 months and had walked at 16 months, but his vocabulary consisted of only two words: "Mama" and "Dadda". His weight was 10 kg. (22 lb.), placing him below the third percentile, and his height 79 cm. (31·5 in.), placing him between the third and tenth percentiles. His head was normal in size and shape, but the ears were low-set, small, and elongated. The broad helix (fig. 3) formed a gothic arch and terminated posteriorly in the skin over the mandibular joint. The triangular fossa of the auricle was reduced in size and the lobule was absent. The scars on the left side of the forehead were described as keloid. There was a suggestion of hypertelorism and epicanthic folds, but otherwise the eyes appeared normal. The palate was high and ogival. Fourteen teeth were present. The neck appeared very short, the loose skin folds on the nape were still present, and the hair was growing cephalad. The lower part of the chest was contracted but it was not shield-like. The nipples were small. The heart was enlarged with a right-ventricular tap. The first sound was split, and the second was loud and single. There was a continuous machinery murmur heard over the right chest and down the left sternal border towards the apex. The pulse-rate was 148 and irregular with several dropped beats. The blood-pressure was 120/60 mm. Hg in his arm and 120/40 in his leg. Both femoral pulses were palpable. The genitalia were male and appeared normal for a child of his age. The penis was circumcised and both testes had descended into the normally developed scrotum.

The hæmoglobin was 12·9 g. per 100 ml. with normal indices. The leucocyte-count was 6000 per c.mm. and the differential count was normal. The specific gravity of the urine was 1·027 and a trace of acetone was present. The electrocardiogram showed biventricular hypertrophy with P-pulmonale. Radiographs of the chest showed cardiomegaly, the configuration of the heart being suggestive of right-chamber enlargement. The vascular pattern was increased mesially and decreased peripherally. An intravenous pyelogram was normal. X-rays of the bones revealed normal maturation. Cardiac catheterisation and cineangiocardiography were performed. These studies indicated a ventricular septal defect and the filling of the pulmonary arteries via a patent ductus arteriosus (pseudotruncus arteriosus). A main pulmonary artery was not identified. The angiocardiogram also suggested a mild narrowing of the isthmus of aorta (Dr. Samuel Kaplan).

On March 15, 1960, the excrescence of the right thumb was amputated, put under sterile conditions into Eagle's medium with 10% bovine serum, and shipped by airmail to Oak Ridge National Laboratory where the tissue was cultured and analysed for chromosomal constitution of the child. The following procedures were employed:

The amputated tissue was cut into small pieces about 0·5–1 mm. in diameter and embedded in plasma-clots. Active cell-proliferation took place within 3 weeks and subcultures were made by trypsinisation. The cell suspension was inoculated into Leighton tubes containing removable coverslips, and the cultures incubated at 37°C. (98·6°F) for 2 days. The cells grown on the coverslip were treated with a colchicine solution brought to a final concentration of 10^{-6} *M* in the culture medium 5–6 hours before fixation. The medium was replaced by a warm hypotonic 0·7% sodium-citrate solution and incubation continued for 30 min. The coverslips were removed from the tubes, assembled in a porcelain staining tray which was placed into a 0·7% sodium-citrate solution containing 1% (v/v) of fixative (3 parts absolute ethyl alcohol/1 part glacial acetic acid) for 5 sec. After this, the tray was carried through three 5-minute changes of the full-strength fixative. Without rinsing in water the coverslips were allowed to dry at room temperature by placing them horizontally, cell-side up, on a sheet of paper. The coverslips were reassembled in the tray and stained for 15 min. in 1% natural orcein in 45% acetic acid. After dehydration by *tert*-butyl alcohol (T.B.A.)—two changes of undiluted T.B.A., followed by T.B.A./xylol 2/1, T.B.A./xylol 1/1, T.B.A./xylol 1/2 (1–2 min. each)—the coverslips were taken through two changes of xylol and were mounted in Canada balsam.

A total of 42 intact metaphase plates were analysed. 40 plates contained 46 chromosomes each with X and Y sex chromosomes. No chromosomal anomalies were apparent in any of the plates analysed. Fig. 5 illustrates the karyotype of the child. Two cells contained 45 chromosomes. Since the missing chromosomes in these 2 plates were different and the Y chromosomes were present in each plate, the defect was probably due to artefacts.

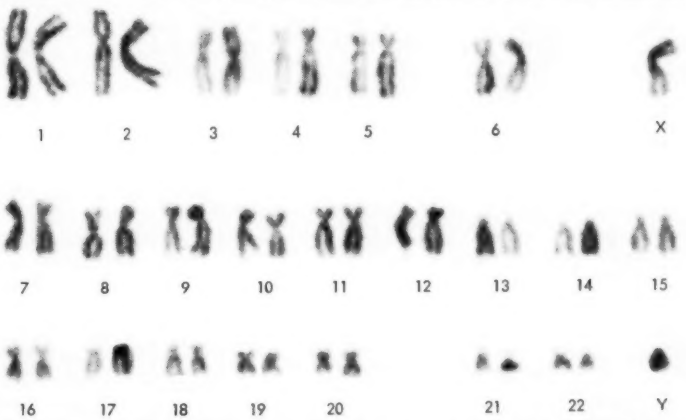

Fig. 5—Karyotype of patient showing 44 autosomes and an X and a Y chromosome (reduced by one-third from ×3500).

Thus, it can be assumed that the karyotype of this child was that of a normal male.

Discussion

Though it has been known that many of the congenital malformations and anomalies characteristic of Turner's syndrome can occur in phenotypical males,[5–7 14 21 22 26 27 29–31 34] chromosome analysis on these "male Turners" had not been reported until a paper on a case of the same syndrome with male phenotype and 45/XO chromosomal constitution appeared.[3] The present finding indicates that a boy with typical Turner's syndrome can have a chromosomal constitution of 46/XY which is the same as that of normal males. No chromosome anomaly was detected.

With the discovery of a 45/XO chromosomal constitution in typical cases of Turner's syndrome with female phenotype, this syndrome and its various components seemed attributable to the missing sex chromosome. But the fact that patients with 45/XO constitution may vary in regard to sex-chromatin [16] and fertility [2] shows that conclusions should be drawn with caution. Ford et al.,[8] Sandberg et al.,[28] Fraccaro et al.,[9] and Chu [4] found in patients with Turner's syndrome an XO/XX-mosaic condition. It appears that even the presence of a portion of XO cells in a body may be responsible for this disorder. Persons with XXX/XO [19] and XY/XO,[18] however, have not been shown to have the stigmata of Turner's syndrome.

Fraccaro et al.[10] found abnormal karyotypes in three women with gonadal dysgenesis who were sex-chromatin positive. All of them have 46 chromosomes including only a single X chromosome and a long, metacentric chromosome which, on morphological evidence, was similar to the chromosomes of pair no. 3. This abnormal chromosome was interpreted as either an isochromosome for the long arm of an X chromosome, translocation of other chromosome material on to an X chromosome, or a trisomic for chromosome no. 3—that is, monosomy for the X chromosome. If the first interpretation, which was considered by Fraccaro et al. as the most likely, is true, the patients are therefore trisomic for the long arms and monosomic for the short arm of X. Harnden and Stewart [17] have reported a case of pure gonadal dysgenesis in a female with primary amenorrhœa who had ovarian hypoplasia but none of the other features of Turner's syndrome. A sex-chromosome constitution of XY was found despite the presence of uterus, fallopian tubes, and vagina. Furthermore, two female patients with a tentative clinical diagnosis of gonadal dysgenesis and with a positive sex-chromatin pattern were found to have a normal female karyotype.[12] Although mosaicism with XO cells has not been completely ruled out in these patients [12 17] and in the present instance, our finding of a boy with XY sex chromosomes showing congenital anomalies usually associated with Turner's syndrome adds further doubt that the entire clinical picture of Turner's syndrome can be attributed to the absence of a second sex chromosome.

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Addendum

We have examined the chromosomes of 50 additional cells in short-term blood-cultures from the patient. The result indicates that 45, XO/46, XY mosaicism in this individual is unlikely.

	No. of chromosomes						
	40	*43*	*44*	*45*	*46*	*47*	*52*
No. of cells	1	1	1	3	39	4	1

Court Brown et al. (*Lancet*, 1960, i, 160) reported seven patients with "male gonadal dysgenesis" in whom the nuclear sex was male and a modal chromosome number of 46 was found. After the present paper had been accepted for publication, a paper by Fraccaro et al. (*Acta endocr.* 1961, **36,** 98) appeared reporting a case of male Turner's syndrome with an apparently normal male karyotype. Steiker et al. (*J. Pediat.* 1961, **58,** 321) have also reported two cases in which the chromosome findings are in accord with this and other reports.

INDUCTION OF TUMOURS IN NEWBORN FERRETS WITH MILL HILL POLYOMA VIRUS

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Mill Hill polyoma virus (M.H.P.) was isolated from the spleen of a mouse with spontaneous leukæmia (Negroni et al. 1959). The virus produces multiple tumours in such rodents as mice, rats, and hamsters after inoculation into newborn or very young animals. Other polyoma virus strains have similar properties, and, in addition, "S.E." polyoma produces papillomas (which subsequently regress) in rabbits (Eddy et al. 1959) and "B.P." virus gives tumours in the multimammate mouse *Rattus natalensis* (Rabson et al. 1960). Hitherto, there have been no reports of the induction of tumours by polyoma virus in any non-rodent species (except rabbits).

TABLE I—TUMOURS* PRODUCED IN MICE AND HAMSTERS BY PHENOL-TREATED M.H.P.

Phenol-treated M.H.P. (< 1 T.C.I.D.)	Animal (newborn)	No. (surviving more than 50 days)	Tumour-bearing	Latent period (days)
Experiment 1	FAK mouse	3	None	..
	C3H mouse	15	8	161, 222, 223, 252, 323, 323, 352, 355
Experiment 2	FAK mouse	7	3†	153, 222, 322
	C3H mouse	6	None	..
	Hamster	4	2‡	99, 112
Experiment 3	Hamster	7	1§	93
Experiments 4–8	Hamster	41	None	..

* There were no leukæmias.
† One dwarf died at 46 days.
‡ One tumour serially transplantable. H.I. antibodies in serum of both.
§ Inoculum was antiserum-treated D.N.A. No H.I. antibodies.

We originally speculated that the resistance of other species to the virus might be immunological, and that the protein-free, infective deoxyribose nucleic acid (D.N.A.) of the agent should be used in attempts to infect such animals. S.E. polyoma virus infective D.N.A. has been described by di Mayorca et al. (1959). Obtained by phenol treatment of the virus, it was cytopathic for mouse-embryo cells in culture. The complete virus was produced by such cultures, and this gave the usual spectra of tumours in rodents. The results of direct inoculation of the D.N.A. into young animals have not been reported.

The D.N.A. prepared by us from M.H.P. has invariably proved cytopathic for tissue-cultures, and, in addition, two preparations have produced tumours in mice and hamsters (table I), and ferrets (table II). There is, as yet, no conclusive evidence that our D.N.A. preparations consist only of D.N.A., and they will therefore be referred to as "phenol-treated M.H.P." Although the infectivity for cultured cells is destroyed by incubation with deoxyribonuclease, there is some evidence that it is also abolished by rabbit anti-M.H.P. antiserum (but not by normal rabbit serum). It is possible, therefore, that some residual antigen is still associated with the phenol-treated virus, sufficient to react with antibody but insufficient to protect the D.N.A. against the enzyme.

The hypothesis that phenol-treated M.H.P. might be infective for species other than rodents may yet be true, but we have also found that M.H.P. itself is capable of producing tumours in ferrets.

Experiments

The ferrets were bred in our animal house from an initial nucleus of six females and two males. Five of the females had two litters each during the year, and the sixth only one. Eighty-seven young were born, and sixty-four were weaned and used in the experiments to be described.

Phenol-treated M.H.P.

M.H.P., and the mouse-embryo cells from which it was derived, were extracted with 90% phenol in the presence of 2% sodium benzoate by the general method described by Kirby (1959). The phenol was extracted from the final aqueous layer with peroxide-free ether, and the ether was removed by bubbling washed nitrogen through the solution. Preparations infective for mouse-embryo tissue culture have also been made with 6% sodium *p*-aminosalicylate instead of sodium benzoate.

Tumour-induction in Ferrets by Phenol-treated M.H.P.

Three ferrets were inoculated subcutaneously (within 24 hours of birth) with 0·1 ml. of the D.N.A. In tissue-culture infective doses (T.C.I.D.) this represents < 1. One ferret was killed when it was 118 days old with a tumour (T1) at the inoculation site. The tumour (T2) in the second was removed surgically 280 days after inoculation. M.H.P. was isolated from one of these tumours, and the other tumour-bearing animal had hæmagglutination-inhibiting (H.I.) antibodies in its serum (table II).

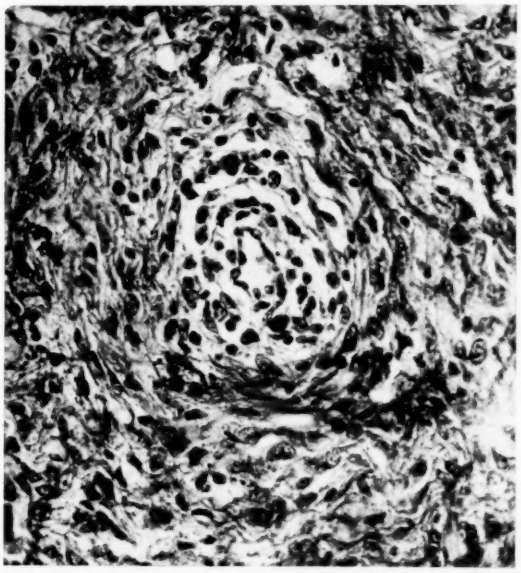

Fig. 1—Ferret T1. Subcutaneous sarcoma showing whorl arrangement of tumour cells around a small blood-vessel. (Weigert's iron hæmatoxylin and van Gieson's stain. Reduced by 1/3 from ×500.)

Histologically T1 showed fusiform sarcoma cells with a few mitoses. The tumour cells appeared to encircle capillaries and small vessels, extending in a circumferential direction (fig. 1). There was local invasion of muscle, but no metastases.

T2 is shown in fig. 2. The excised tumour appeared to have two different zones, one hard and one soft. Histologically the former was a fusiform-cell sarcoma similar to T4 and T5 (see below). The soft tumour, composed of stellate and fusiform cells in a myxoid stroma, merged at the boundary with the adjacent fibrosarcoma.

Transplantation.—Attempts to passage T1 in adult ferrets or

TABLE II—PRODUCTION OF TUMOURS IN FERRETS INOCULATED WHEN NEWBORN WITH M.H.P. AND PHENOL-TREATED M.H.P.

Inoculum	Dose (T.C.I.D.)	Route	No. of ferrets	Tumours and induction period (days)	Transplantability (1st passage)	M.H.P. present	H.I.-antibodies	No. and age (days) of survivors
Phenol-treated M.H.P.	< 1	Subcutaneous	3	T1 (*118*) T2 (*264*)	1/8 ferrets ..	+ Under test	Not tested 1/800	1 (*302*)
M.H.P.	10^7	Subcutaneous	5	None	..	–	..	5 (*168*)
M.H.P.	10^7	Intraperitoneal	24	T4 (*152*) T5 (*176*)	1/4 hamsters ..	+ Not tested	1/800 1/800	21* (*219–284*)
Control	..	..	22†	None	..	–	Nil ‡	22 (*175–560*)

* One M.H.P.-treated non-tumour-bearing ferret was killed after 271 days; the serum-H.I. titre was 1/200.
† Six of these were inoculated when 1 day old with 0·1 ml. culture fluid from mouse-embryo cells.
‡ In the single animal tested.

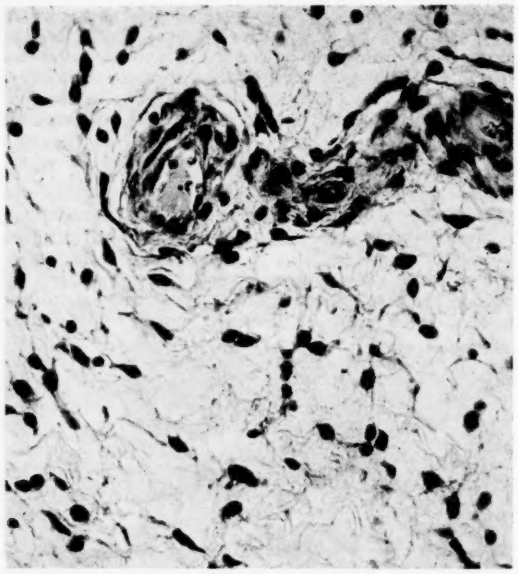

Fig. 2—Ferret T2. Stellate and fusiform cells in the myxoid stroma of the soft part of the fibrosarcoma. (Hæmatoxylin and eosin. Reduced by 1/3 from ×500.)

Fig. 3—Ferret T4. Necropsy appearance of the abdomen showing the cut surface of the tumour arising from the left posterior abdominal wall.

in newborn or adult hamsters were unsuccessful. A tumour (T3), however, arose in one out of eight 5-day-old ferrets 84 days after implantation of the graft, and this was removed surgically on the 94th day. Histologically it resembled T1.

Later attempts at passage of T3 in hamsters have been unsuccessful. In view of the genetic disparity among the ferrets, and between ferrets and hamsters, these results are scarcely surprising.

Tumour Induction in Ferrets by M.H.P.

Four different M.H.P. preparations of known virus titre were used in this series. The twenty-nine ferrets were 1–2 days old. In three experiments the animals were inoculated by the intraperitoneal route, and in the fourth subcutaneously.

The results are shown in table II. Two tumours were produced (T4 and T5) after 152 and 176 days respectively. One tumour was assayed for and found to contain M.H.P., and the serum of the same animal had H.I. antibodies to the virus.

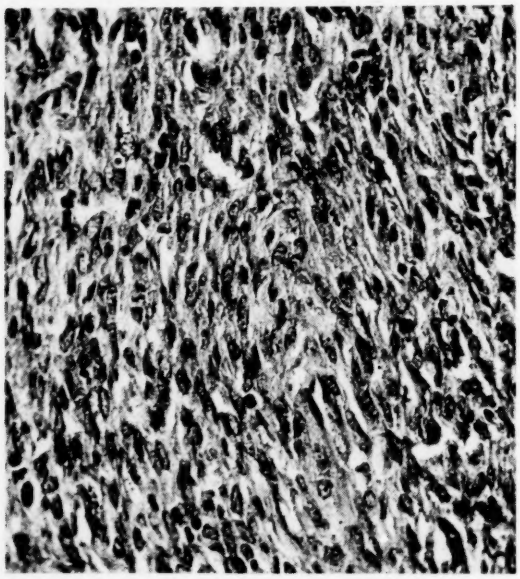

Fig. 4—Ferret T4. Section of the tumour shown in fig. 3. (H. & E. Reduced by 1/3 from ×500.)

Histologically T4 was a fibrosarcoma, which arose in the left posterior abdominal wall and invaded the adjacent normal muscle (figs. 3 and 4). There were no metastases. T5, which arose in the right posterior abdominal wall, was larger than T4, and showed a number of necrotic areas. Histologically the two tumours were identical.

Transplantation.—An attempt to passage T4 in adult ferrets was unsuccessful, but the tumour grew slowly in one (T6) out of four hamsters inoculated when 3 days old, and it became palpable in 78 days. Although this tumour was histologically similar to T4, the possibility exists that it arose by infection of hamster cells by M.H.P. liberated from the graft. Further passage of T6 in newborn hamsters has apparently failed. T5 has been passaged in fourteen newborn hamsters; but, after 44 days, no tumours are palpable.

Discussion

There are three reasons for attributing these ferret tumours to the action of M.H.P. or of its infective D.N.A.:

1. Reports of spontaneous tumours in young ferrets are rare. Rewell (1949) described multiple squamo-sebaceous carcinomas of the skin in a male polecat, which was at least 6 years old. In a survey published in 1959, Lombard and Witte recorded one sarcoma of the orbit in a female polecat at the Philadelphia Zoo. Another skin carcinoma was observed by Symmers and Thomson (1950); and, later (1953), they described multiple carcinomas with focal mast-cell accumulations in the skin of a mature female ferret. They also described tumours in three other female ferrets—i.e., a papillary tubular cystadenoma of the kidney, a multilocular bileduct cystadenoma of the liver, and a lymphoblastic lymphosarcoma. These workers have seen a variety of ferret tumours since 1950, but Prof. W. St. C. Symmers (personal communication) has not observed subcutaneous fibrosarcomas in young ferrets.

2. M.H.P. was recoverable from each of the two tumours tested.

3. The serum of all of three tumour-bearing animals contained H.I. antibodies to the virus.

One puzzling feature will be re-examined when new-

born ferrets become available again this month. Apparently the tumour response of very young ferrets to M.H.P. (or M.H.P.D.N.A.) is independent of the number of T.C.I.D. (for mouse-embryo fibroblasts) inoculated between the limits of 1 and 10^7. It is possible, of course, that M.H.P. preparations contain a very small amount of a mutant virus infective for ferrets. If this is so, then one must further postulate that it is either stable to phenol or that the infective D.N.A. obtained from it is more stable than that from the rest of the M.H.P.

The biochemical and immunological properties of phenol-treated M.H.P. will be reported separately.

Summary

Mill Hill polyoma (M.H.P.) virus (and phenol-treated M.H.P.) produces sarcomas after inoculation into newborn ferrets. M.H.P. virus has been isolated from all the tumours tested, and the serum of tumour-bearing ferrets contained H.I. antibodies. Tumours also arise in mice and hamsters inoculated, when newborn, with phenol-treated M.H.P.

We are particularly grateful to Miss G. Adams for her assistance with the biochemistry; to Mr. J. Menzies for his great care of the ferrets; and to Mr. E. V. Willmott and Mr. A. J. Pringle for the photographs.

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THE ÆTIOLOGY OF HIMALAYAN ENDEMIC GOITRE

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THE mountain slopes of the Himalayas, Alps, Pyrenees, and Andes have been the world's most notorious foci of endemic goitre (Kelly and Snedden 1958). The northern frontiers of the Indian subcontinent extending from Kashmir in the west to Bengal and Assam in the east form an extensive Himalayan goitre belt (fig. 1). The pioneering work of Sir Robert McCarrison focused attention not only on the extent of the Himalayan endemic but also on its cause and on the reaction of the thyroid to various noxious influences—nutritional, toxic, or infective. McCarrison introduced the concept of goitre " noxa " and thought in terms of the " lifeline " of the thyroid gland (Sinclair 1953).

Despite all that has been written about the ætiology of endemic goitre, many problems remain unsolved. The study by Stanbury et al (1954), the first of its kind, of the metabolism of iodine in endemic goitre in western Argentina, employing radioactive iodine and modern chemical methods of assay of stable iodine, indicates that lack of iodide in the diet is the most probable cause. Similar observations have been made in other areas, such as Venezuela, Holland, and Finland, though those from Italy do not seem to fit in with this hypothesis (Stanbury 1958b). Besides supporting the iodide-deficiency hypothesis, the work of Stanbury et al. has thrown light on the mechanism of adaptation of man to iodide deficiency.

Recent evidence suggests that the iodide-deficiency hypothesis cannot explain endemic goitre in every area and that other factors may be significant. A naturally occurring goitrogenic substance has been isolated from human foods (Greer and Astwood 1948), and Clemments (1955) has discovered that endemic goitre among children in Tasmania is due to ingestion of a goitrogenic substance capable of interfering with the iodide-trapping mechanism of the thyroid. There are other scattered observations which, though less conclusive than those of Clemments, nevertheless incriminate factors other than iodide deficiency (Tolly 1951, Steyn 1955, Hettche 1956).

The cause of Himalayan endemic goitre is obscure.

The early chemical studies of McCarrison on the iodide content of soil and water provided no evidence to support the iodide-deficiency hypothesis (McCarrison et al. 1927). McCarrison's extensive investigations indicated that infection with organisms of the coli group might be the causal factor (McCarrison 1917). In later work he suggested that faulty and unbalanced diets played a leading part (McCarrison and Madhava 1932). Soon afterwards Stott et al. (1931), working in another Himalayan endemic zone (Uttar Pradesh), concluded that the drinking of hard water containing excessive amounts of calcium was of ætiological importance. This supports the belief that calcium may be a goitrogenic factor, and recalls the conclusion arrived at a century earlier in India by McClelland (1835) on the basis of extensive medicotopographical studies. More recently Wilson (1941) suggested that excessive intake of fluorine might be a causal factor in the Punjab, where she found a close association between the incidence of endemic goitre and fluorosis.

In this paper we present the results of a preliminary inquiry into some relevant aspects of iodine metabolism in this condition.

Material and Methods

Material

The study was made in two areas of the sub-Himalayan goitre belt (fig. 1). Area I is a township, Pathankot, in the Punjab State. Area II is a township, Bettia, in the Bihar State. The two areas are about 600 miles apart. Both are in the heart

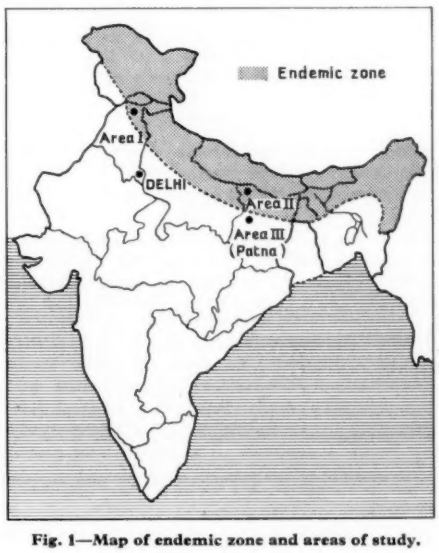

Fig. 1—Map of endemic zone and areas of study.

TABLE I—GROUPS OF CHILDREN INCLUDED IN THE STUDY

Locality	Age-range (yr.)	Sex	No.	Status of goitre				
				Diffuse, smooth, and symmetrical				Asymmetrical and/or nodular
				−	+	++	+++	
Area I (endemic)	12–16	M	15	..	5	8	1	1
	12–16	F	18	..	9	7	2	..
Area II (endemic)	8–12	M	30	..	4	6	4	16
	8–12	F	13	..	5	3	1	4
Area III (control)	12–14	M	9	9	..	..	..	..
	14–15	F	9	9	..	..	..	..

The goitre is classified, after Murray et al. (1948), as:
+ Just visible, diffuse, symmetrical.
++ Clearly visible, diffuse, symmetrical.
+++ Very clearly visible (Rosetti neck), diffuse, symmetrical.
− Indicates absence of visible goitre.

of the goitre belt; earlier surveys among schoolchildren showed a goitre prevalence between 50 and 60% in area I, and of almost 100% in area II. Schoolchildren, aged 8–16 years, who had lived in the areas for at least five years and who had visible goitres of varying grades were included in the study. Schoolchildren of comparable age in area III, the city of Patna in the Bihar state, were studied as controls on whom similar measurements were made (fig. 1). Area III, which is known to be free from endemic goitre, is about 150 miles from area II, is physically contiguous with it, and its population is akin in their way of life to that in area II. Thrs is the nearest good control that could be obtained. Some information about the persons studied and their goitre status is given in table I. All the children studied were euthyroid. Some adult men and women in areas I and II (permanent residents) were also studied at the same time, and the results were compared with those obtained among adults in Delhi, another non-endemic area (fig. 1).

Methods

In each of the areas a field laboratory was set up where in-vivo counts of ^{131}I uptake by the thyroid were made. Blood-sera for

TABLE II—^{131}I UPTAKES IN THE ENDEMIC AND CONTROL AREAS

Locality	Sex	2-hour uptake (%)		6-hour uptake (%)		24-hour uptake (%)	
		No. studied	Mean uptake with S.D.	No. studied	Mean uptake with S.D.	No. studied	Mean uptake with S.D.
Area I (endemic)	M	..		..		15	70·0 ±11·9
	F	..		11	39·3 ±12·3	18	56·2 ±17·4
Area II (endemic)	M	30	55·9 ±16·96	30	67·1 ±12·57	28	68·6 ±12·1
	F	13	54·1 ±24·54	13	67·1 ±22·01	12	73·1 ±18·15
Area III (control)	M	9	10·6 ± 4·2	..		9	39·9 ±12·9
	F	9	8·7 ±2·9	..		9	38·2 ± 4·1

the estimation of protein-bound iodine (P.B.I.) were transported immediately to our laboratories in Delhi where the actual estimations were made within a matter of 3 or 4 days after collection.

30 μC of ^{131}I was given in 100 ml. of water to each person and the uptake by the thyroid was determined by measuring the activity over the thyroid with the aid of a high-efficiency γ-ray detector attached to a Geiger-Müller counter. The tube was kept at a constant distance of 6 in. from the isthmus of the thyroid gland. The counts were made in all cases at the end of 24 hours, and in many at 2, 6, 12, and 48 hours. Background counts were made at each time-interval, and these were subtracted from the neck counts. Radioactive decay of the isotope was corrected for by measuring the counts of the standard ^{131}I in a phanto-cube at intervals. The results were expressed in terms of percentage of radioactivity taken up by the thyroid out of the total dose administered. Serum-P.B.I. was determined according to the method of Barker et al. (1951).

The effect of potassium thiocyanate (KCNS) on ^{131}I uptake was studied in 4 persons with endemic goitre. The drug was given by mouth during the rising phase of uptake and a watch was kept over the thyroid at intervals for evidence of release of ^{131}I from the gland. 2 persons received 0·5 g., and the other 2 had 1·0 g. each.

The effect of large doses of potassium iodide by mouth on the ^{131}I uptake was studied in 5 persons whose uptake pattern was determined earlier. 3 persons received 5 mg. of potassium iodide each as a single dose, and the other 2 had 10 mg. each. 24 hours after the administration of the drug, the uptake pattern was again determined.

Goitre was graded clinically by following in principle the classification proposed by Ryle and his colleagues (Murray et al. 1948). A distinction was made qualitatively between smooth symmetrical diffuse enlargements and asymmetrical nodular ones. This distinction seems basic to the understanding of the natural history of endemic goitre (Ramalingaswami 1958).

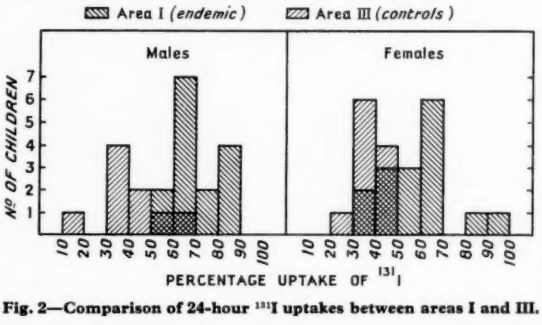

Fig. 2—Comparison of 24-hour ^{131}I uptakes between areas I and III.

The size of the goitre itself was arbitrarily classified into mild (+), moderate (++), and very large (+++).

Results

^{131}I Uptake Pattern

The 24-hour uptakes of ^{131}I in the children in the three areas are shown in table II and graphically in figs. 2 and 3. It is obvious that children with endemic goitre in areas I and II have increased avidity of the thyroid for iodine compared with those from the non-endemic control area, III. The mean 24-hour uptake value in the endemic areas (I and II) was 62·5% and 69·9% respectively in comparison with the mean value of 39·05% in the control area, III. The difference in uptakes is very striking, most of those with endemic goitre having uptakes much above the highest value observed in the control group.

The 2-hour and 6-hour uptakes indicate the speed with which ^{131}I is removed from the circulation and taken up by the thyroid (table II). The differences in the 2-hour uptakes between endemic area II and the control area (III) are most pronounced, there being scarcely any overlap between the two sets of data. In 30 out of 43 cases, the

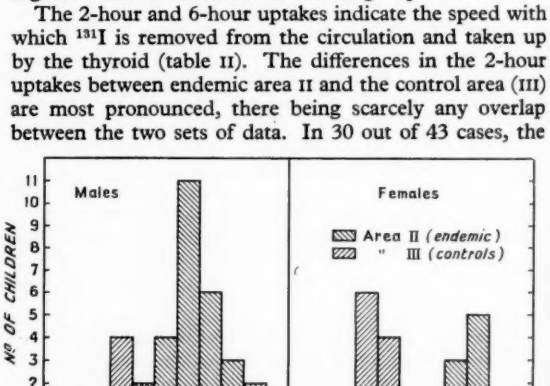

Fig. 3—Comparison of 24-hour ^{131}I uptakes between areas II and III.

TABLE III—SERUM-P.B.I. LEVELS IN ENDEMIC AND NON-ENDEMIC GROUPS

Serum-P.B.I. level (μg. per 100 ml.)	No. of persons		
	Endemic area		Non-endemic area
	Children	Adults	Adults
0–1	..	3	..
1–2	4	3	..
2–3	6	2	..
3–4	5	4	..
4–5	..	..	6
5–6	2	1	2
6–7	..	..	..
7–8	..	..	1
Mean value ..	3·00 μg.	2·33 μg.	5·1 μg.
Range	(1·2–6·0 μg.)	(0·4–5·6 μg.)	(4·1–7·4 μg.)
S.D.	±1·43	±1·55	±1·37

2-hour uptakes exceeded 50%, and in 22 of them even 60%, of the dose administered. In 8 cases they were close to 24-hour uptakes. Unfortunately, 6-hour-uptake measurements in the control group (area III) were not possible. The mean 6-hour uptakes of 67·1% for males and females in endemic area II are abnormally high by any standard. Thus, in a group of 181 euthyroid persons with no goitre, McConahey et al. (1956) found a mean value of 14·9% as the 6-hour thyroid uptake, 95% of the values lying between 7·5 and 25·0%.

Protein-bound Iodine

Table III shows the values for P.B.I. in goitrous persons in areas I and II compared with those in euthyroid persons with no goitre from the Delhi area. Blood samples could not be collected from the children in the control area (III), and so the values in endemic area are compared with those from another non-endemic area (Delhi). It is significant that 15 out of 17 children with endemic goitre had P.B.I. values below the lowest value found in the control group. By contrast, none of the controls had values less than 4 μg.

TABLE IV—24-HOUR ^{131}I UPTAKE IN RELATION TO STATUS OF GOITRE

Locality	Sex	Status of goitre					
		Mild		Moderate to severe		Nodular or asymmetrical	
		No. examined	Uptake of ^{131}I	No. examined	Uptake of ^{131}I	No. examined	Uptake of ^{131}I
Area I	M	7	69·7	7	71·4	1	63·0
	F	9	48·1	9	64·3	..	..
Area II	M	4	74·8	9	74·3	15	63·7
	F	5	79·1	3	81·1	4	60·2

It must be remembered, however, that the values from Delhi relate to adults, and therefore the two sets of data may not be strictly comparable. For a similar reason, we have refrained from comparing the values from areas I and II with those in euthyroid persons from other parts of the world.

Iodine Metabolism and State of Goitre

We tried to find out whether the nature of the thyroid enlargement was related to the activity of the gland as measured by the uptakes (table IV). In those in which asymmetry and nodular development had taken place the uptakes were variable and somewhat lower than in those, of comparable size, with no nodularity. Nevertheless, the uptakes in the nodular goitres were still considerably higher than in normals. In adults, however, where the nodularity, asymmetry, and pathological alterations in the thyroid were greater, the uptakes had fallen in many cases to within normal limits.

Effect of Potassium Thiocyanate

Fig. 4 shows the ^{131}I-uptake pattern in 2 representative cases with endemic goitre after the administration of 0·5 g. and 1·0 g. of KCNS during the rising phase of uptake. Clearly no release of trapped iodide has taken place and the curve assumes a plateau after the administration of KCNS.

Effect of ^{127}I Supplement

Fig. 5 shows ^{131}I curves of 2 persons with endemic goitre who initially had high uptakes and to whom a single large dose of potassium iodide had been administered. A single dose of 5·0 mg. of potassium iodide reduces the uptake to within normal limits. The effect is more noticeable with 10·0 mg. dose.

TABLE V—^{131}I UPTAKES IN ADULTS WITH ENDEMIC GOITRE

Uptake of ^{131}I (%)	6-hour uptakes (no. of persons)		24-hour uptakes (no. of persons)	
	Endemic	Non-endemic (Delhi)	Endemic	Non-endemic (Delhi)
0–10	1	6	1	..
10–20	2	5	1	..
20–30	2	1	2	6
30–40	9	..	10	4
40–50	4	..	1	2
50–60	3	..	6	..
60–70	..	..	..	..
70–80	..	..	..	..
80–90	1	..	1	..
90–100	..	..	..	..
Mean	37·30	11·3	40·90	31·3
Range	6·0–82·0	6·0–25·0	7·2–82·0	22·0–40·0
S.D.	±15·06	±5·41	±15·47	±7·27

Adults with Endemic Goitre

22 adults in areas I and II were studied at the same time as the children. All had large long-standing goitres, distorted by nodularity, asymmetry, and cystic change. In sharp contrast to the children, their maximum uptakes were not uniformly raised; and, in many cases, these fell below 50% (table V). The measurements were made with the subjects seated in front of the counter in as nearly as possible the same position as the children; but the large size of the goitres obscured neck landmarks to such an extent that the position can only be regarded as approximate. Slight shifts in the position of the subject sometimes resulted in considerable variations in counts, and, when different portions of the goitre were presented to the tube, widely variable counts were observed. "Cold", "warm", and "hot" nodules were easily shown.

Serum-P.B.I. was determined in 13 persons with goitre, and in all except 1 the level was below 4 μg. per 100 ml.,

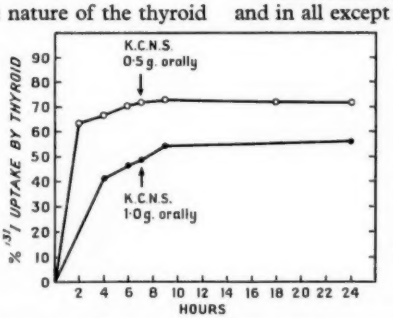

Fig. 4—Effect of potassium thiocyanate (KCNS) on ^{131}I uptake in endemic goitre.

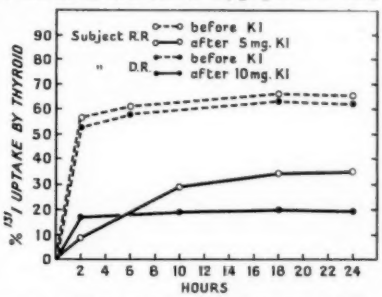

Fig. 5—Effect of ^{127}I supplement on ^{131}I uptake in endemic goitre.

whereas none of the adults from the non-endemic area had a P.B.I.-level less than 4 μg. (table III).

Discussion

This study was concerned chiefly with children of school age in two areas in the heart of the Himalayan endemic belt, and with children of similar age from a non-endemic area adjacent to the goitre belt. The children from the endemic areas all had goitres; those from non-endemic area had no visible or palpable thyroid enlargement. Both groups were clinically euthyroid.

The results clearly show increased avidity of the thyroid for iodine and low serum-P.B.I. levels in children with endemic goitre, compared with the controls. In 11 children with endemic goitre in whom 24-hour urine collections could be regarded as accurate, the 24-hour urinary excretion of ^{127}I was less than 10·0 μg. 2 members of the field-investigating team from Delhi with no thyroid enlargement and 24-hour ^{131}I uptakes of 25 and 13% excreted during the same period 27·7 μg. and 63·82 μg. of ^{127}I respectively. These findings, taken together, seem consistent with the hypothesis that in the two areas studied the endemic is probably related causally to a deficiency of iodide in the body. It should be emphasised that the patients did not change their dietary habits, and were studied in their own environment. If goitrogenic factors depressing iodide uptake played any part, they should have been revealed under the conditions of this study.

The results of thiocyanate administration also indicate that there is no block in the utilisation of inorganic iodide trapped by the gland. The depression of ^{131}I uptake to within normal limits after administration of a single dose of 5 mg. or more of potassium iodide may indicate that this amount was sufficient to replenish the iodine stores and that it is some measure of the degree of iodide deficit. Possibly, however, this effect may be due to other factors. In Stanbury's experience with the Argentina endemic, when a single dose of 5 mg. of iodide was given the capacity of the gland to take up iodide became extremely limited, and above this level no further iodide found its way into the gland (Stanbury et al. 1954).

Our results show the severity of the endemic in the two areas studied, particularly area II. This is borne out by the high incidence of goitre (100% in schoolchildren in area II), by the development of nodular asymmetrical goitre during childhood in some cases, by the invariable presence of nodularity among the adults, and by the tendency for the P.B.I. to fall below the lower limit of normal. In some children, 2-hour uptakes exceeded 50% of the administered dose.

The low P.B.I. values found in some goitrous children is at variance with the finding of values within normal limits in the endemics of Argentina, Holland, Finland, and Italy (Stanbury 1958a). Considerable attention was paid to P.B.I. estimation in the present study, and periodic checks on duplicates showed agreement. We believe that, in the light of other data collected in this study, the low P.B.I. values should be interpreted as reflecting the intensity of iodide deficiency. It is surprising that, with such low levels of P.B.I., the children showed no gross evidence of hypothyroidism. They were all attending school and did not appear to be physically retarded in comparison with children of similar age and economic status from non-endemic areas. Possibly, however, a more detailed study of these children might reveal defects of mental and physical development. Our findings agree with the low P.B.I. and butanol-extractable-iodine values reported by Raman and Beierwaltes (1959) in another Himalayan endemic area, further to the east, bordering on Burma.

All the goitrous adults had huge goitres, grossly altered by nodularity and cystic change. The lack of consistency in their uptakes is perhaps understandable in the light of Taylor's finding that such thyroids show unevenness of uptake of iodine and incorporation into hormone (Taylor 1953). There was a distinct lowering of the P.B.I. values, the depression being more severe than in the children. The ^{131}I uptakes and P.B.I. levels in goitrous adults, compared with goitrous children, are consonant with the assumption that the picture in adults represents the continuation of the process initiated in childhood, with varying degrees of degenerative alteration supervening over a period.

The present study provides a basis for the belief that, in the areas studied, supplementation of the diet with iodine in some form or other would be the most rational procedure for large-scale prevention. Even though McCarrison and Madhava (1932) looked for factors other than iodide deficiency to explain the complex picture of Himalayan endemic goitre, neither he or Stott et al. (1931) denied the value of iodide prophylaxis.

Summary

Endemic goitre pervades the entire northern border of the Indian subcontinent and is one of the most notorious endemics in the world. Its cause is not known with certainty.

Some aspects of iodine metabolism were investigated in two widely separated endemic areas of this region, and the results were compared with those in a contiguous control area, free from the endemic. The study was made chiefly on schoolchildren aged 8–16 years, and the investigations included measurement of ^{131}I uptake by the thyroid and determination of serum-protein-bound iodine (P.B.I.)

The results showed increased avidity of the thyroid for iodine in endemic goitre associated with low serum-P.B.I. levels. The results are consistent with the view that the Himalayan endemic in the two areas is probably causally related to an environmental iodide deficiency. They also show that the deficiency is extreme.

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EXPERIMENTS WITH TRACHOMA VACCINES

Experimental System Using Inclusion Blennorrhœa Virus

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TRACHOMA is one of the remaining major problems of world public health. Affecting enormous numbers of people in countries where hygiene is poor, it is probably the most common single cause of blindness and impaired vision. In its earlier stages it is amenable to antibiotic and sulphonamide therapy, but treatment is much more difficult when severe cicatrisation and corneal damage have occurred. The most satisfactory method of eradication would be the universal raising of hygienic standards to a level at which trachoma no longer flourished, but this ideal is unlikely to be realised in the foreseeable future. Mass treatment campaigns have been instituted in several countries since the war, but their long-term efficacy depends largely on keeping the people at risk under continual treatment for considerable periods—a difficult task even under favourable conditions, and perhaps impossible in countries with scattered populations and poor communications.

For these reasons, a vaccine affording protection during the early years of life, when trachoma is most commonly acquired, would be of great help in controlling its spread. The development of such a vaccine was not practicable until the causal agent had been isolated and grown in quantity in the laboratory. This was accomplished as recently as 1957, when T'ang and coworkers in Pekin isolated viruses from trachoma patients by inoculating conjunctival material into the chick-embryo yolk-sac. Morphologically, these agents resemble the psittacosis-lymphogranuloma viruses, and possess the same group antigen. T'ang's findings were confirmed in the Gambia by Collier and Sowa (1958). Ætiological relationship to trachoma was proved by inoculating two African strains into the eyes of human volunteers, in whom all the cardinal signs of trachoma were induced, and in whose conjunctivæ the characteristic Halberstaedter-Prowazek inclusion bodies were repeatedly demonstrated (Collier and Sowa 1958, Collier, Duke-Elder, and Jones 1958, 1960).

Although trachoma virus can now be grown in quantities sufficient for making vaccines, prophylaxis by this method is arguable, since the ophthalmic disease induces little or no immunity to reinfection, an observation confirmed experimentally by direct eye-to-eye inoculation (see Julianelle 1938) and by using virus grown in chick embryos (Thygeson et al. 1960). Serological confirmation of the poor immune response in natural trachoma was obtained by agglutination (Bernkopf et al. 1960b) and complement-fixation tests (Grayston et al. 1960). These findings are consistent with the confinement of the infecting virus to superficial epithelial cells, and the consequent absence of a general stimulus to antibody formation. Parenteral injection of a suitable antigen might, however, elicit an immune response. This supposition prompted the experiments to be described.

Experimental System

The first requisite was a suitable experimental animal. Although mice can be infected with certain strains of virus inoculated by various routes (Bernkopf 1959, Hurst and Reeve 1960), it was thought preferable to assess experimental vaccines by directly measuring their power to protect against conjunctival infection, which is possible only in primates. We chose baboons, which are known to be susceptible to conjunctival inoculation with material from the eyes of trachoma patients (Julianelle 1938).

The second requisite was a strain of virus that would consistently induce easily recognisable physical signs *associated with characteristic epithelial-cell inclusion bodies*. Simians are liable to conjunctival folliculosis of unknown ætiology which has often been confused with experimental trachoma; the differential diagnosis has recently been discussed in an excellent paper by Thygeson et al. (1960). The presence of Halberstaedter-Prowazek inclusions with carbohydrate matrices is pathognomonic of trachoma or inclusion blennorrhœa, and we regard their demonstration as an essential criterion of specific infection of simian species with either of these viruses.

Artificial Infection of Baboons

Attempts were made to infect baboons with the G1 strain of virus that had induced trachoma in a human volunteer after 8 passages in chick embryos. Two *Papio hamadryas* and three *P. papio* were inoculated respectively with virus from the 11th and 13th chick-embryo passage. None became infected. 1 *P. hamadryas* and 1 *P. papio* were then inoculated with virus isolated directly from the volunteer by chick-embryo inoculation. Unequivocal infection was induced only in the *P. papio*. Although inclusions were numerous, many were atypical; the elementary bodies varied greatly in size and staining characteristics (fig. 1), and strikingly resembled those found in the early stages of antibiotic treatment (Bietti 1945, Gilkes et al. 1958a). This suggested faulty replication of the G1 strain of trachoma in an unfavourable environment, and precluded its use in baboon experiments.

During 1959 and 1960, several agents were isolated from patients with inclusion blennorrhœa. Two of them were described by Jones, Collier, and Smith (1959). They are identical with trachoma virus in morphology and staining characteristics and possess the same complement-fixing group antigen; indeed, apart from their greater pathogenicity for baboons, it has so far been impossible to distinguish them from trachoma virus by any test at our command, including cross-neutralisation in tissue culture (Reeve and Graham, unpublished).

One of these viruses (strain LB1) was passaged 8 times in chick embryos, and inoculated into the eyes of four baboons.

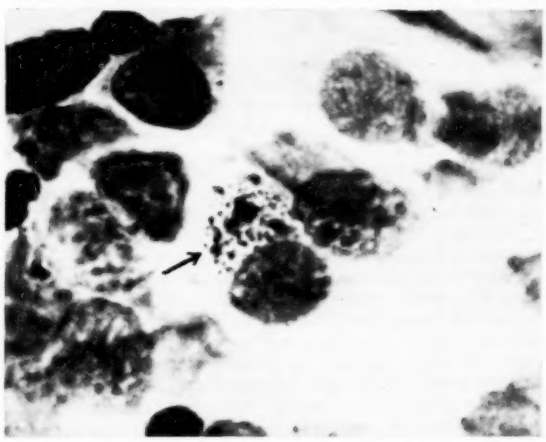

Fig. 1—Conjunctival scraping from baboon infected with the G1 strain of trachoma. Arrow indicates epithelial cell inclusion with grossly irregular elementary bodies. Stained Giemsa-May-Grünwald (×1050).

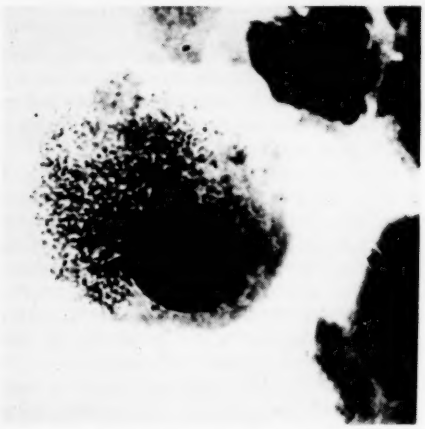

Fig. 2—Epithelial cell inclusion from conjunctiva of baboon infected with inclusion blennorrhœa virus, strain LB4. The cytoplasm contains a mass of regular elementary bodies. Stained Giemsa-May-Grünwald (×1050).

It induced severe follicular conjunctivitis in all of them, and numerous inclusions, morphologically identical with those found in humans with trachoma or inclusion blennorrhœa, were repeatedly demonstrated during the course of the disease.

The close relation of inclusion blennorrhœa virus to trachoma, and its pathogenicity for baboons, suggested its use in an experimental system for research on trachoma vaccines. A group of baboons was vaccinated with LB1 antigen, and then challenged by conjunctival inoculation with the homologous strain, now in its 18th egg passage. Unexpectedly, the virus failed to infect both immunised and unvaccinated control animals; this and other experiments showed that the LB1 strain had become avirulent for the baboon conjunctiva between its 8th and 18th passage in chick embryos. Since no early egg-passage virus was available, vaccine experiments with this strain were abandoned.

Another virus (strain LB4) isolated from a baby with inclusion blennorrhœa was inoculated into baboons after either 2 or 4 chick-embryo passages. Although the severity of infection was less than with 8th-passage LB1 virus, strain LB4 consistently induced follicular conjunctivitis with typical inclusion bodies (fig. 2). In subsequent vaccination tests, therefore, material from the 2nd and 4th egg passages was used for challenge.

Vaccination Experiments

Materials and Methods

Baboons.—Young baboons (*P. cynocephalus*) weighing about 3 kg. were used. In experiment 1, manipulations were made under ethyl-chloride/ether anæsthesia. Subsequently, anæsthesia was induced by intramuscular injection of 20 mg. 'Sernyl'.

Phosphate buffered saline (P.B.S.) (Dulbecco and Vogt 1954) and *sucrose/potassium-glutamate solution* (S.P.G.) (Bovarnick et al. 1950) both contained streptomycin sulphate 200 μg. per ml.

Infectivity titrations.—Tenfold serial dilutions of virus suspensions were made in S.P.G.; 0·3 ml. amounts of each dilution were injected into the yolk-sacs of five 6-day chick embryos, which were then candled daily. Embryos dying within 48 hours were discarded. Yolk-sacs were removed from embryos dying subsequently, and from survivors on the 10th day after inoculation. Smears made from them were stained with Giemsa and examined microscopically for the presence of elementary bodies. 50% end-points were calculated by Kärber's method, and are expressed as $E.I.D._{50}$ per ml. of original suspension (E.I.D. = egg infectious doses).

Antigen LB4/V1 (experiment 1).—Yolk-sacs heavily infected with the 5th chick-embryo passage of LB4 virus were used. The membranes, weighing 24 g., were shaken mechanically in a 250 ml. conical flask with 60 ml. P.B.S. for 30 minutes at 4°C. After being strained through two layers of gauze to remove the membranes, the crude virus-containing fluid was centrifuged at 100*g* for 10 minutes. (All centrifugations were done at 4°C.) The supernatant fluid was removed and held at 4°C and the deposit resuspended in 100 ml. P.B.S. and centrifuged as before. The virus was deposited from the two pooled supernatants by angle centrifugation at 3600*g* for 45 minutes and resuspended in 9 ml. S.P.G. This suspension was clarified by three successive centrifugations at 1000*g* for 10 minutes, the deposit being resuspended in 9 ml. S.P.G. on each occasion and finally discarded. The pooled clarified supernatants constitute the vaccine. A Giemsa-stained smear revealed enormous numbers of elementary bodies with comparatively little debris. After seeding on appropriate media for aerobic and anaerobic sterility tests, the vaccine was ampouled in 1 ml. amounts, frozen rapidly at −70°C, and held at that temperature until required. The infective titre of a thawed ampoule was $10^{7\cdot0}$ $E.I.D._{50}$ per ml.

Control vaccine used in experiment 1 was prepared from 24 g. of normal yolk-sac by an identical method.

Antigen LB4/V6 (experiment 2) was prepared by a less elaborate method, all low-speed centrifugation being omitted. After initial extraction of 14 g. of membranes by shaking and straining, the virus was deposited by high-speed centrifugation, dispersed in 10 ml. S.P.G. with an M.S.E. blender, made up to 50 ml. with S.P.G., and ampouled and stored as previously. Its infective titre was $10^{5\cdot2}$ $E.I.D._{50}$ per ml.

Conjunctival challenge.—All animals were challenged 10 days after the final dose of vaccine by firmly rubbing the upper and lower fornices of the right eye with a small cotton-wool swab soaked in virus suspension. The virus used in experiment 1 was from the second chick embryo passage of strain LB4, with a titre of $10^{8\cdot0}$ $E.I.D._{50}$ per ml. That in experiment 2 was a semi-purified pool of 2nd and 4th passage LB4 virus containing $10^{4\cdot9}$ $E.I.D._{50}$ per ml.

Examination for inclusions.—Conjunctival scrapings from the upper and lower fornices were each spread over an area of about 1 sq. cm., and stained for inclusions by a method based on that of Rice (1936) and Gilkes et al. (1958b). The smears were treated with 1% iodine in 2% potassium iodide for 15 minutes, blotted on filterpaper and covered with a thin film of immersion oil. The entire area was scanned at a magnification of ×180, and the inclusions counted. In the event of doubt about the identification of an iodine-stained inclusion, its position was noted; after decolorisation with methyl alcohol and restaining with Giemsa-May-Grünwald, it was again examined.

In experiment 1, all smears were examined by me. Subsequently, examinations were shared with Dr. W. Blyth, the slides being marked in code by a third person. Every negative or doubtful smear was checked by the other examiner.

Course of Infection in Unvaccinated Baboons

Observations of 19 *P. cynocephalus* inoculated with the 2nd or 4th egg passage of LB4 virus indicated considerable variation in host response, and emphasise the importance of using adequate numbers of animals for assessing the results of protection tests.

Physical signs are as follows:

(*a*) *External signs* of inflammation (œdema of the lids and purulent discharge) occur only in severe infection with LB4. By contrast, both signs are pronounced in infections with early egg passages of LB1.

(*b*) *Conjunctival hyperæmia* is seen within a few days of inoculation and may persist for several weeks. It is usually maximal during the 2nd week, when the conjunctivæ are red and velvety.

(*c*) *Infiltration and œdema* of the conjunctivæ and subjacent tissues is fairly constant; it is most pronounced during the first 7–10 days, and gradually subsides during the next few weeks. Hyperæmia, œdema, and infiltration are usually greater, or at least more easily seen, in the upper lid. Injection of the upper tarsal conjunctiva is particularly characteristic.

(*d*) *Follicular hyperplasia.*—In man this is a cardinal sign of trachoma and inclusion conjunctivitis, but in simian species its significance cannot be assessed without critical examination. In a proportion of otherwise normal baboons and monkeys, superficial translucent follicles, 0·5–1 mm. in diameter, are present in the fornices or at the inner or outer angles, but almost never encroach on the upper tarsal conjunctiva. Occasionally, somewhat larger and deeper follicles are seen in the lower fornix. They are usually scanty and may persist only for days or weeks. The surrounding conjunctiva appears normal. This condition is the "non-specific" or "spontaneous" folliculosis mentioned above. Thygeson et al. (1960) recently described another type of follicular hyperplasia in *Macacus cynomolgus* associated with conjunctival inflammation which they term "spontaneous follicular conjunctivitis". Neither form is associated with the presence of epithelial-cell inclusions.

Nevertheless, a form of follicular hyperplasia developing as a response to specific infection can be distinguished. The follicles are most pronounced and easily recognised in the lower lid; they are deeper set, larger, and more florid than the non-specific variety, often attaining 2 mm. in diameter. In the upper lid, the appearance after inoculation of numerous rather superficial follicles under a hyperæmic conjunctiva suggests specific infection with inclusion conjunctivitis virus. Such follicles are often opaque and may be distinctly yellowish.

Follicular hyperplasia may occur as early as the first week after inoculation, but typically attains its full development some weeks later and then regresses over a period of months. In figs. 3 and 4 the small superficial follicles thought to be more characteristic of "spontaneous" folliculosis are appropriately distinguished.

Virological signs.—The most important and unequivocal sign of specific infection is the presence of Halberstaedter-Prowazek inclusions in the conjunctival epithelial cells. Chick-embryo inoculation is a more sensitive indicator of the presence of virus in man (Sowa and Collier 1960), but virus isolation from baboons is often spoilt by bacterial contamination, usually with coliform organisms.

The total inclusions in upper-lid and lower-lid scrapings from the inoculated eye were recorded at each examination. This is, at best, a roughly quantitative method, since the number of epithelial cells obtained varies considerably. Nevertheless, there is some correlation between number of inclusions and severity of the clinical signs. Inclusions usually persist for about a month after inoculation and are rarely found by the 6th week.

To summarise, the most usual finding after inoculation of LB4 virus into the eye is conjunctivitis of moderate severity, proceeding to follicular hyperplasia that is most pronounced in the lower lid. The inflammatory signs persist for some weeks, and follicles for months. Corneal lesions are not observed. Inclusions are usually most numerous during the first 2 weeks, and persist for about a month. Occasionally, however, a mild infection only is induced, with scanty inclusions. It must nevertheless be emphasised that inclusions were always found at some stage in every unvaccinated animal.

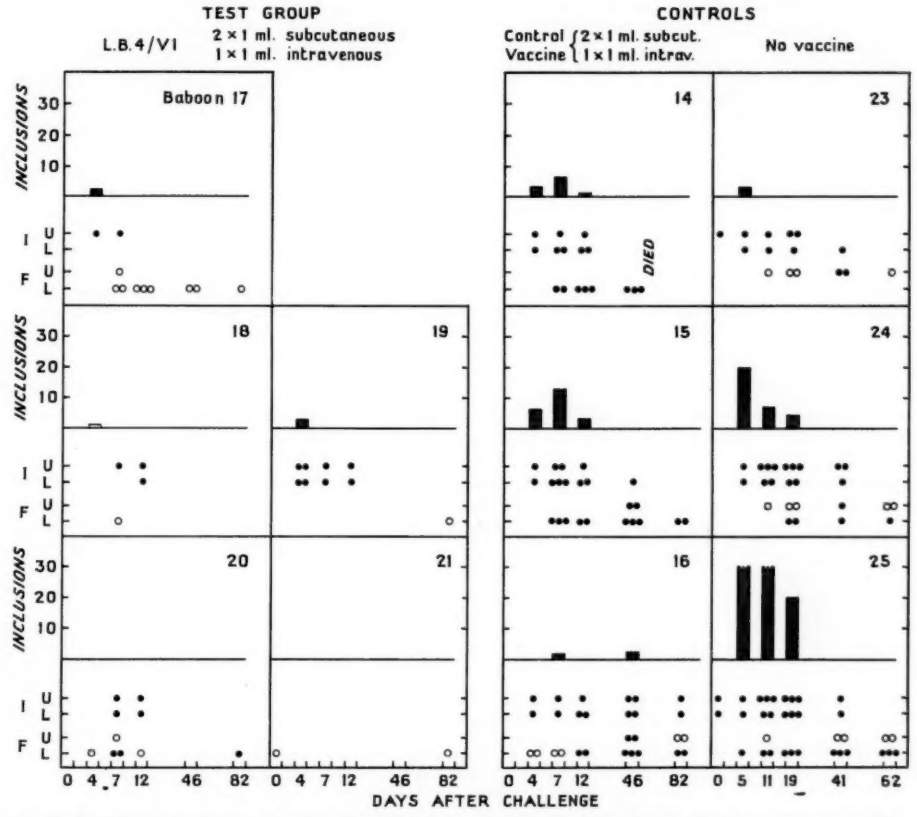

Fig. 3—Experiment 1. Response of vaccinated and control animals to conjunctival challenge (right eye only).

I = inflammation (conjunctival hyperæmia, œdema, and infiltration).

F = follicles { ● large, deep. ○ small, superficial

U = upper lid.

L = lower lid.

● = slight, scanty.

● ● = moderate.

● ● ● = severe.

▒ Inclusions identified with certainty.

▭ Possible inclusion, not confirmed with Giemsa.

EXPERIMENT 1

This was designed to test the response to conjunctival inoculation of LB4 virus after vaccination with a live antigen prepared from the homologous strain.

Test group.—Five baboons (nos. 17–21) received at weekly intervals three 1 ml. doses of vaccine LB4/V1, the first two doses subcutaneously and the last intravenously. The subcutaneous doses were injected in two 0·5 ml. amounts into both axillæ, slightly different sites being chosen for the second injections. There were no observable local or general reactions to vaccination.

Control groups.—Four animals (nos. 13–16) received a similar course of control (normal yolk-sac) vaccine. No. 13 died during the immunisation period. Fortunately more baboons then became available, and three more animals (nos. 23–35) were taken into the control series, although they did not receive a course of control vaccine.

After challenge the animals were examined at the intervals shown in fig. 3, the physical signs being recorded on each occasion without reference to previous notes. One control animal died under anæsthesia on D46 (D=days after challenge).

In this and the following experiment, a number of animals had scanty small superficial follicles of the "spontaneous" type in both eyes on the day they were challenged. These have not been recorded in figs. 3 and 4.

Results.—There was no significant difference in response to challenge between the unvaccinated group and that receiving control vaccine. No. 23 sustained a mild infection only; the other five baboons all had moderate or severe infections. Inclusions were present in all animals, and persisted for at least 12 or 19 days, except in no. 23.

In the group receiving live vaccine, the clinical signs were much less severe. Early inflammation was absent in one animal and in the rest it tended to be less in degree and duration. Especially noticeable was the failure to proceed to late follicular hyperplasia. Virological evidence of protection was even more striking. Unequivocal but scanty inclusions were found only in two baboons on D4, but not thereafter. A scraping from another on that day revealed one possible inclusion in a clump of cells, which stained too densely with Giemsa to permit confirmation.

These findings provided clear evidence of a protective effect. The second experiment was designed to confirm them, and to assess the protection afforded by subcutaneous injection alone.

EXPERIMENT 2

Group A.—Six baboons (nos. 29–34) received a course of injections like that in experiment 1, using antigen LB4/V6.

Group B (nos. 35–40) were immunised as group A, except that the final intravenous dose was replaced by a subcutaneous dose, also of 1 ml.

Control group (nos. 41–46) received no vaccine.

Results (fig. 4).—Moderate or severe infections were induced in five of the unvaccinated animals, three of which had external œdema of the upper lid and purulent discharge on D4. The uninoculated eye of no. 46 became infected and inclusion positive between D17 and 24. The sixth baboon had a mild infection. Inclusions persisted in all the control animals for at least 17 days.

In group A, two animals remained free of inflammation and the remainder had only slight and transient signs.

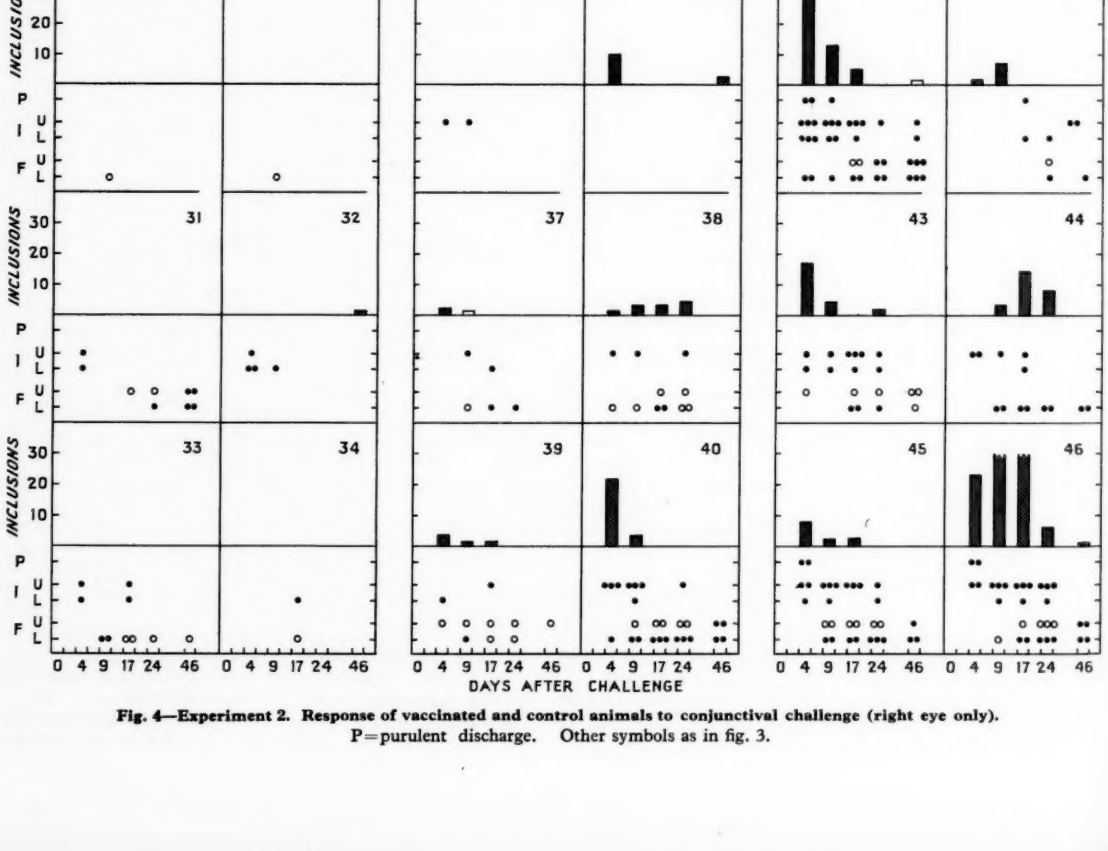

Fig. 4—Experiment 2. Response of vaccinated and control animals to conjunctival challenge (right eye only).
P=purulent discharge. Other symbols as in fig. 3.

Characteristic late follicles were seen in only one of this group. Five of them were inclusion-negative throughout.

In group B, no. 35 had slight transient hyperæmia, and remained free of inclusions. No. 36 was free of clinical signs throughout, but was inclusion-positive on two occasions. Nos. 37, 38, and 39 had mild infections; only no. 40 matched the average severity of infection in the control series. There was a tendency for inclusions to be fewer and to disappear sooner than in the control group.

It is interesting that two immunised animals (nos. 32 and 36) were inclusion-positive 46 days after challenge; at this time the appearance of the eyes and the cytology of conjunctival scrapings were normal. The three inclusions found in these two animals stained both with iodine and with Giemsa, but their appearance was atypical. That found in no. 32 had elementary bodies of somewhat irregular size, and those in no. 36 stained poorly with Giemsa.

This experiment confirmed the high degree of protection conferred by two subcutaneous and one intravenous dose of live antigen; it also demonstrated partial protection with three subcutaneous doses.

A detailed report of the cytology and serology will be presented in a later paper.

Discussion

These experiments provide unequivocal evidence that protection against infection with the trachoma/inclusion-blennorrhœa viruses can be attained by parenteral immunisation. Inclusion blennorrhœa virus was used in preference to trachoma because of the greater pathogenicity of the LB4 strain for baboons; nevertheless, we believe these agents to be so closely related that inferences drawn from the behaviour of one may almost certainly be applied to the other. Until recently, inclusion blennorrhœa virus was believed to differ from trachoma in its ability to infect simians. Even this distinction is now blurred by the report of Thygeson et al. (1960) that two strains of trachoma isolated in the U.S.A. cause an infection in *M. rhesus* and *M. cynomolgus* indistinguishable from experimental inclusion blennorrhœa—an observation that opens the possibility of protection experiments with trachoma strains pathogenic for apes or monkeys. Our own preliminary experiments, not reported here, suggest that immunisation with a trachoma antigen confers at least partial protection against challenge with inclusion blennorrhœa virus. It is not yet clear whether lack of complete protection reflects a true immunogenic difference in the strains used, or the use of an antigen of lower titre than those described in this paper.

The only previous account of experiments with trachoma vaccines prepared from cultured virus is that of Grayston et al. (1960) in Formosa:

> The serological response of human volunteers to injections of various antigens showed that virus adsorbed to aluminium hydroxide provoked higher titres of complement-fixing antibody than did purified live or formolised antigens. The authors suggested, without giving details, that in three volunteers receiving vaccine during the course of experimental infection there was more clinical improvement than in three unvaccinated subjects. They also tested the capacity of live and formolised vaccines to protect monkeys against conjunctival challenge. A total of six animals, including two controls, were used to test two antigens; the results suggested modification of the clinical course in three of the vaccinated monkeys and complete protection of the fourth.

Because of the small number of animals and the variation in response to conjunctival inoculation observed by Thygeson et al. (1960) and by myself, it is difficult to assess the significance of this result. Furthermore, the sole criterion of infection was the appearance of follicular conjunctivitis, and no reference is made to examination for inclusion bodies.

It is apparent that further laboratory work is desirable before embarking on large field trials. More information is needed about the immunising properties of different strains, and of live and inactivated vaccines prepared by various methods. We may, for example, look forward to replacement of yolk sac antigens by virus grown in tissue culture (Bernkopf et al. 1960a, Furness, Graham, Reeve, and Collier 1960), since such material is more readily purified.

The optimal quantity, spacing, and route of injection of vaccine must also be determined. Our experiments indicate that a final intravenous dose, impracticable in human vaccinations, confers greater protection than subcutaneous injection alone. An attempt must be made to overcome this difficulty by different spacing of injections, or by the use of more potent antigens. It must be remembered, however, that in these experiments the animals were challenged by rubbing a highly infective virus suspension into the conjunctiva—a far more severe test of immunity than anything likely to be encountered under natural conditions—and it is possible that the response induced by subcutaneous or intramuscular injection alone would be acceptable for human immunisation.

In the absence of other signs, the finding of scanty inclusions in two vaccinated animals 6 weeks after challenge (experiment 2) suggests a latent infection, a phenomenon known to occur with other viruses of the psittacosis-lymphogranuloma group (Bedson 1938).

On the duration of artificially induced immunity there is, as yet, no information; but experiments are in progress to answer this and the other outstanding questions. It is also desirable to devise a serological test that will indicate the state of immunity. That this is possible with the complement-fixation tests used hitherto is by no means certain. Assays of serum neutralising antibodies in mice (Bernkopf 1959) or cell cultures (Reeve and Graham, unpublished), may be useful in this respect.

Summary

The efficacy of trachoma vaccines is best tested in primates, which alone among laboratory animals are susceptible to conjunctival infection. When simians are used, they must be challenged with a strain of virus capable of inducing follicular conjunctivitis clinically and virologically distinguishable from the "spontaneous" folliculosis to which they are liable.

In baboons the G1 strain of trachoma virus was insufficiently pathogenic, but a closely related inclusion-blennorrhœa virus caused an easily recognisable conjunctival infection associated with typical inclusion bodies in epithelial cells. Baboons were immunised with live vaccines prepared from this virus, and challenged by conjunctival inoculation with the same strain. Virtually complete protection was attained with two subcutaneous and one intravenous dose and partial protection with three subcutaneous doses. There were no untoward reactions to the vaccine.

These experiments show the possibility of active immunisation against the trachoma/inclusion-blennorrhœa viruses. It is hoped that they will contribute to development of a trachoma vaccine for field use.

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TREATMENT OF ACUTE EXPERIMENTAL CARBON-MONOXIDE POISONING WITH OXYGEN UNDER PRESSURE

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As a result of the investigations of Haldane from 1895 onwards the harmful and often fatal effects of carbon monoxide even at low concentrations in the inspired air have been attributed to the much greater affinity of hæmoglobin for this gas than for oxygen. In addition, as shown by Douglas et al. (1912), carboxyhæmoglobin alters the dissociation curve of the remaining oxyhæmoglobin, impeding oxygen release to the tissues. Even at 50% saturation of the blood with carboxyhæmoglobin, the remaining oxyhæmoglobin does not unload oxygen to the tissues until their oxygen tension is very low. The degree of hypoxia reached is therefore greater than it would be in a simple anæmia with a hæmoglobin content reduced to 50% of normal.

Therapy is based on the removal of carbon monoxide from the body via the lungs. To this end, the administration of oxygen under pressure might be expected to have some advantages. Thus, by increasing the amount of oxygen dissolved in the plasma, the deleterious effect of carboxyhæmoglobin on oxygen liberation from the remaining oxyhæmoglobin would be circumvented. In addition, the removal of carbon monoxide from combination with hæmoglobin would be hastened.

Investigations were, therefore, carried out on:

1. The effect of increased oxygen pressure on rodents gassed with carbon monoxide.

2. The effect in vitro of exposure to air, oxygen, or oxygen at 2 atmospheres pressure, on carboxyhæmoglobin with reference to the speed of liberation of carbon monoxide.

3. The speed of removal of carbon monoxide from dogs gassed with this substance, and afterwards exposed to air, oxygen, 'Carbogen' (5% carbon dioxide + 95% oxygen), or oxygen at 2 atmospheres pressure absolute.

Effect of Oxygen under pressure on Carbon-monoxide Poisoning in Rodents

Rats and cavies were used. The animals were placed in a pressure vessel with a transparent lid of 1 in. thick 'Perspex'. Carbon monoxide was added to the air-filled chamber to give a concentration of 3%. Oxygen could be admitted to raise the pressure in the chamber to 15 lb. per sq. in. above atmospheric. Three groups of experiments were done.

Group A.—12 rats and 3 cavies were exposed to 3% carbon monoxide in air. The rats showed ataxia after 2 minutes; they were unconscious by 3–4 min., and died in 5–13 min. (mean $7^1/_2$ min.). The times for the cavies were 3, 5, and 15 min. Immediately after death, the carbon-monoxide content of the heart-blood was determined by the volumetric method of Van Slyke in 5 rats and 2 cavies.

Group B.—12 rats and 3 cavies were rendered unconscious by exposure to 3% carbon monoxide in air; oxygen was then admitted to the chamber to raise the pressure to 15 lb. per sq. in. above atmospheric. This resulted in recovery in $^1/_2$–1 min., with the animals fully conscious in 1–3 min., though carbon monoxide was still present in the chamber in its original amount. Immediately after decompression at the end of a further 10–15 min., 5 rats and 2 cavies were killed, and the heart-blood analysed.

Group C.—12 rats and 3 cavies were exposed to 3% carbon monoxide in air, but oxygen was added simultaneously to the chamber to raise the pressure to 15 lb. per sq. in. above atmospheric. All animals remained conscious and showed normal alert behaviour, for periods up to 3 hours. After decompression 5 rats and 2 cavies were killed and the carbon-monoxide content of the blood determined.

Results.—From these experiments the following facts emerge:

1. The concentration of gas used was rapidly fatal.

2. By administering oxygen under pressure these fatal effects could be prevented. If the animals had lost consciousness, they could be revived.

These protective effects might be explicable on the basis that enough oxygen was dissolved in the animal's plasma to supply the body needs for oxygen. But the animals from group B and C did not become unconscious on removal from the tank containing carbon monoxide and oxygen under pressure, but continued normal activity in ordinary room air, suggesting that simple solution of oxygen in the plasma was not the sole factor responsible for their improved or protected state. It seems that in addition, by increasing the oxygen tension in these animals, a possibly small but biologically significant amount of the carboxyhæmoglobin had been broken down to yield more hæmoglobin for oxygen carriage.

ANALYSIS OF HEART-BLOOD

Groups	Oxygen capacity (vol. %)	Carbon monoxide (vol. %)	Available oxygen (vol. %)
Rats:			
A	25·3	21·2	4·1
B	16·6	8·4	8·2
C	19·4	12·0	7·4
Cavies:			
A	16·6	13·0	3·6
B	17·3	10·7	6·6
C	15·8	9·7	6·1

To test this hypothesis, heart-blood from animals in each of the three groups was analysed for carboxyhæmoglobin content by the volumetric method of Van Slyke, immediately after removal of the animals from the chamber. The results of these analyses are shown in the table.

The amount of oxygen carried by the hæmoglobin in groups B and C is twice that in group A, both in rats and cavies. This may be interpreted as indicating that oxygen under pressure not only yields beneficial results by increased plasma carriage of the gas, probably in solution, but also alters the equilibrium mixture of carboxyhæmoglobin and oxyhæmoglobin in favour of a higher yield of the latter as would be expected from the Law of Mass Action.

Speed of Liberation of Carbon Monoxide from Human and Equine Blood when exposed directly to Air, or to Oxygen at 1 and 2 Atmospheres

20 ml. samples of fresh heparinised human and horse blood were exposed to coal-gas by bubbling for 20 minutes. 3 ml. samples were then placed into glass boiling-tubes of 1 in. internal diameter. When these were mounted almost horizontally and rotated once every 10 seconds, the blood-samples filmed over 20 sq. in. of internal surface. There was free exchange of gases through the open ends of the tubes. 6 such tonometers were used for each experiment on each blood-sample. The whole was encased in a large polyethylene bag with entrance and exit ports through which air or oxygen could be passed at a rate of 5 litres per min. In the experiments with oxygen under pressure the tonometers were placed in a pressure vessel. By determining the carboxyhæmoglobin content at various times the dissociation-rates could be plotted. The ambient temperature was 20–22°C (68–72°F). The carboxyhæmoglobin contents were determined both by the volumetric method of Van Slyke and Neill (1924) and by the spectrophotometric method of King and Wootton (1956). A rough check was made by the pyrogallol/tannic-acid method of Sayers and Yant (1925).

Results.—Fig. 1 shows the results graphically. Both human and equine bloods containing high levels of carboxyhæmoglobin appear to lose carbon monoxide slowly when filmed in air, faster in 1 atmosphere of oxygen, and fastest in 2 atmospheres of oxygen.

Speed of Removal of Carbon Monoxide from Blood of Dogs breathing the Gas and afterwards exposed to Air, Carbogen, or Oxygen at 1 and 2 Atmospheres Pressure

Healthy mongrel dogs weighing about 15 kg. were lightly anæsthetised with intravenous pentobarbitone sodium, 20 mg. per kg. body-weight. The trachea was intubated with a cuffed Magill tube connected to a 2-litre rebreathing bag with a soda-lime canister interposed. Oxygen could be added intermittently to replace that used up, and small amounts of carbon monoxide could be added to the bag over the course of 1 to 2 hours. During this time the formation of carboxyhæmoglobin was observed by withdrawing blood-samples from the region of the right atrium by a polyethylene catheter inserted through the right external jugular vein. These 4 ml. blood-samples were heparinised, and the carboxyhæmoglobin content determined with a Hartridge reversion spectroscope and by the volumetric method of Van Slyke.

In 4 dogs inhaling carbon monoxide for periods from 1 to 2 hours considerable respiratory depression occurred. At this point, using artificial respiration (Stephenson respirator) the animals were made to inspire air, carbogen, or oxygen at 1 and at 2 atmospheres pressure, at a flow-rate of 6 litres per min.

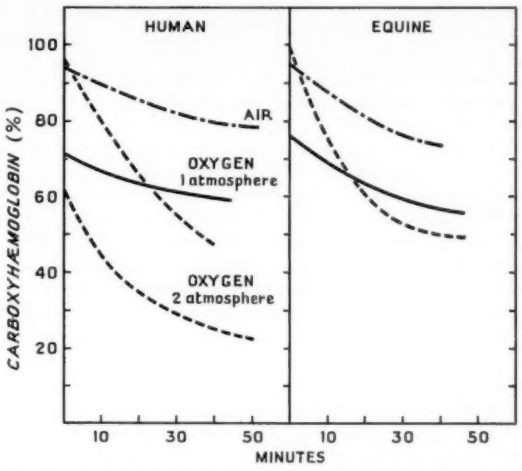

Fig. 1—Rate of breakdown of carboxyhæmoglobin in human and equine blood in vitro at 20°C when exposed to either air or oxygen at 1 and 2 atmospheres pressure.

Samples of blood analysed for carboxyhæmoglobin content allowed the rate of disappearance of this substance from the circulation to be determined.

Results.—Fig. 2 shows the carboxyhæmoglobin content of the blood, determined from the samples removed at various times after the end of exposure to carbon monoxide. The use of the Stephenson respirator in the near-apnœic dog produces the most rapid lowering of the carboxyhæmoglobin content of the blood when the animal is breathing oxygen at 2 atmospheres absolute pressure. The rate is distinctly slower when oxygen at normal atmospheric pressure or carbogen are used. Air alone is the least effective agent.

Discussion

When blood is exposed to a mixture of carbon monoxide and oxygen the proportion of hæmoglobin combined with either gas depends on their partial pressures and upon a constant which expresses the relative affinity of hæmoglobin for the two gases (Haldane and Smith 1897). Under the usual circumstances of carbon monoxide poisoning in air, the affinity of hæmoglobin for carbon monoxide is about 250 times that for oxygen.

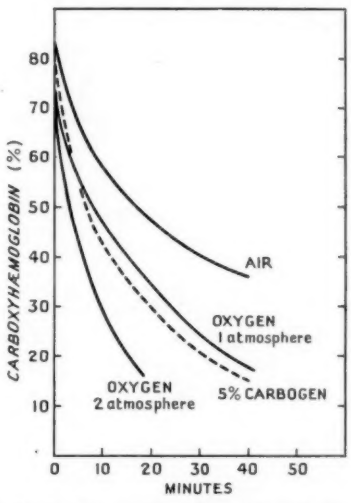

Fig. 2—Rate of breakdown of carboxyhæmoglobin in dogs to breathing air, 5% carbogen, or oxygen, at 1 and 2 atmospheres pressure.

The resulting carboxyhæmoglobin acts mainly by preventing the normal carriage of oxygen by the blood and is widely held not to be a direct tissue toxin.

Nevertheless at a relatively high partial pressure, carbon monoxide can interfere with the enzymatic oxidative systems of the tissues (J. B. S. Haldane 1927). More recent work by Halperin et al. (1959) suggests that even at very low concentrations in the body the gas may have toxic effects.

Just as there is combination with hæmoglobin so is there with myoglobin, though the affinity of carbon monoxide for this is less than for hæmoglobin. This combination in the muscles of the body may account for much of the extreme muscular weakness which is such a prominent symptom of carbon-monoxide poisoning. Similarly, the adverse effect of this combination on the maintenance of adequate function in the cardiac muscle must be significant in determining the survival-time in any case of gas poisoning.

Clearly, then, any treatment of carbon-monoxide poisoning must be directed towards adequate oxygenation of the tissues and rapid elimination of the gas from the body. This necessitates dissociation of carbon monoxide from combination with hæmoglobin and myoglobin, transport to the lungs by an adequately functioning cardiovascular system, and excretion at the lungs by an adequate rate of ventilation.

Though in the less severe case of poisoning, removal to fresh air may be all that is required, our experiments show that in a severe degree of poisoning the twin aims of immediate adequate oxygenation of the tissues and rapid elimination of the gas can be carried out more effectively by using artificial respiration with oxygen at a pressure of 2 atmospheres absolute. We have already used such a technique successfully on persons poisoned with carbon monoxide (Smith and Sharp 1960).

Summary

The harmful and often fatal effects of carbon monoxide, even at low concentrations in the inspired air, have been attributed to the greater affinity of hæmoglobin for this gas than for oxygen. Carboxyhæmoglobin is known to alter the dissociation curve of the remaining oxyhæmoglobin, thus impeding oxygen release to the tissues. In addition, and even at very low concentrations in the body, the gas may have toxic effects.

The treatment of carbon-monoxide poisoning must be directed to adequate oxygenation of the tissues and to rapid elimination of the gas from the body.

The administration of oxygen under pressure seems to be a logical form of treatment, and this was confirmed by investigations on animals. Oxygen, given at a pressure of 2 atmospheres absolute, prevented the otherwise fatal effects of an atmosphere containing 3% carbon monoxide.

This technique has already been used successfully on persons poisoned with carbon monoxide.

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"... At school or office, lavatory accommodation is often inadequate. ... A society widely addicted to purgation has provided itself with meagre facilities for enjoying the results."
—Dr. ABRAHAM MARCUS, *Observer*, March 12, 1961, p. 35.

ANTAGONISM OF INSULIN BY ALBUMIN

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INSULIN increases the glucose uptake of isolated rat diaphragm. Vallance-Owen et. al (1958) reported that the albumin fraction of human serum inhibits this insulin effect. This albumin-fraction antagonist was more active in sera from young diabetic patients requiring insulin than in normal sera. It was found to be absent after pituitary ablation.

We have investigated the effect of albumin on the increase of glucose uptake by rat epididymal fat in response to insulin. We used this tissue because fat has been shown to be more sensitive than muscle to physiological concentrations of insulin (Martin et al. 1958). Albumin did not inhibit the response of fat to insulin. Like Vallance-Owen and his colleagues, we have shown that albumin inhibits the response of muscle to insulin. We have found, however, that this albumin effect is not dependent on the pituitary.

Method

Blood was taken after an overnight fast. Soluble insulin was withheld from the one diabetic patient for 18 hours. The patients after pituitary ablation had received no cortisone for periods up to 72 hours. The blood was allowed to clot and the albumin fraction was extracted from the serum immediately by the method of Debro et al. (1957), or the serum was stored at −5°C for later extraction. Sera from 5 normal subjects, and from 7 patients after pituitary destruction, were studied. In addition, a diabetic patient was examined before and after hypophysectomy.

Rat Diaphragm

Hemidiaphragms from rats fasted for 24 hours were incubated in the buffer of Gey and Gey (1936), as described by Vallance-Owen and Hurlock (1954). Five to ten rats were used for each experiment. Glucose was estimated by a glucose oxidase-peroxidase enzyme system with ortho-dianisidine as the

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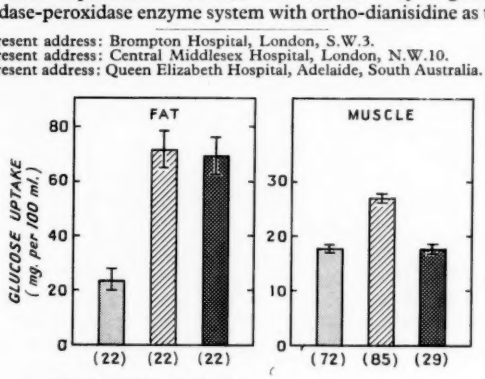

Fig. 1—Effect of albumin on glucose uptake of fat and muscle in response to insulin.

Figures in parentheses indicate number of observations. Mean glucose uptakes expressed as mg. per 100 ml. change in concentration of incubating medium per 10 mg. dry weight of muscle per 90 min., and mg. per 100 ml. change per 100 mg. wet weight of fat per 120 min., ±S.E.M.

TABLE I—EFFECT OF ALBUMIN ON CARBON-DIOXIDE PRODUCTION BY FAT IN RESPONSE TO INSULIN

—	No albumin, no insulin (12)	Insulin 1000 micro-units per ml. (12)	Albumin 3·5–4 g. per 100 ml., insulin 1000 micro-units per ml. (20)
Mean carbon-dioxide production, expressed as counts per min. of barium carbonate per 100 mg. fat ± S.E.M.	1·2 ± 0·04	6·2 ± 0·51	6·2 ± 1·53

Figures in parentheses indicate number of observations.

indicator dye (Huggett and Nixon 1957). For the glucose measurement, the whole incubating medium (2 ml.) was diluted with 48 ml. of distilled water. Proteins were precipitated by adding 5 ml. of this dilution to 0·5 ml. of 25% trichloracetic acid. 0·5 ml. of the supernatant fluid was added to 4 ml. of enzyme solution. After incubation at 37°C for 1 hour, the colour was determined by spectrophotometry. All estimations were duplicated.

Rat Epididymal Fat

For each experiment, two to three rats weighing 150–180 g. were used. They were not starved. The epididymal fat pads

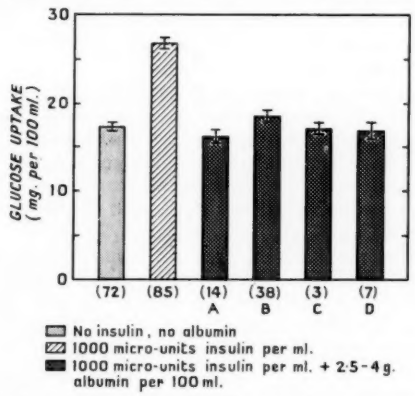

Fig. 2—Effect of pituitary destruction on albumin antagonism of the muscle response to insulin.

A, albumin from 2 hypophysectomised patients; B, albumin from 3 patients with yttrium implants; C, albumin from 1 patient with pituitary-stalk section; D, albumin from 1 patient with Sheehan's syndrome.

Figures in parentheses indicate number of observations. Mean glucose uptakes expressed as mg. per 100 ml. per 10 mg. dry weight of muscle per 90 min., ± S.E.M.

were excised and floated out in buffer solution. Three pieces of similar area and thickness were cut from each fat pad. The fat was incubated in 1 ml. of the buffer solution for 2 hours, and the glucose was estimated in the same way.

Insulin stimulates the conversion of glucose carbon to carbon dioxide by fat, and the effect of albumin on carbon-dioxide production was also investigated. Tracer doses of radioactive glucose-1-^{14}C were used by a method based on that of Martin et al. (1958). Production of carbon dioxide by muscle in response to insulin was too small for satisfactory measurement.

Results

Albumin inhibited the glucose uptake of muscle in response to insulin, so that uptake in the presence of both insulin and albumin did not differ significantly from the basal level (fig. 1). The insulin effect on glucose uptake by fat was not affected by albumin; and the production

TABLE III—EFFECT OF HYPOPHYSECTOMY ON INSULIN ANTAGONISM BY ALBUMIN FROM A DIABETIC PATIENT

Mean glucose uptake (mg. ± S.E.M.)	No insulin, no albumin	Insulin 1000 micro-units per ml.	Insulin 1000 micro-units per ml., albumin 3·5–4 g. per 100 ml.
Before hypophysectomy	13·0 ± 0·44 (8)	24·3 ± 1·73 (8)	21·2 ± 2·06 (8)
After hypophysectomy	16·8 ± 1·70 (12)	26·9 ± 1·44 (12)	21·2 ± 1·64 (12)

Figures in parentheses indicate number of observations. The glucose uptake is expressed in mg. per 100 ml. change in concentration of incubation medium per 10 mg. dry weight of diaphragm muscle per 90 min. ± S.E.M.

of carbon dioxide by fat in response to insulin was also unaffected by albumin (table I).

The muscle response to insulin was still inhibited by the albumin fraction after hypophysectomy, or pituitary destruction by other means (fig. 2). In the 7 patients studied, the clinical picture and biochemical studies confirmed extensive pituitary damage (table II).

The serum of 1 diabetic patient was examined before and after hypophysectomy, in addition to those of the 7 patients shown in fig. 2. With this patient's albumin, alone of all the 13 sera studied, inhibition of the muscle response to insulin was incomplete (table III). Effective hypophysectomy did not alter the inhibitory activity of the albumin fraction.

Albumin alone, without insulin, did not affect the glucose uptake of muscle. The glucose uptake of fat was increased twofold by albumin alone, compared with a sixfold increase with 1000 micro-units insulin. This stimulation of fat by albumin probably results from attached insulin, which albumin antagonism renders ineffective in the muscle experiments.

Discussion

Epididymal fat shows a greater glucose uptake than diaphragm in response to physiological concentrations of

TABLE II—EVIDENCE OF PITUITARY DESTRUCTION

Cases	17-ketogenic steroids (mg./24 hr.)		17-ketosteroids (mg./24 hr.)		24 hr. radio-iodine uptake (%)		Time off cortisone	Withdrawal symptoms
	Before	After	Before	After	Before	After		
1. Pituitary-stalk section	..	..	..	0·8	43	8	48 hr.	+
2. Hypophysectomy	..	..	..	4·4	22	<5	on	−
3. ,,	5·3	..	14·3	4·9	..	..	on	−
4. Yttrium implant		1·0		4·0				
,, ,,		1·0		1·0	33 (48 hr.)	9·2 (4 hr.)	5 days	+
5. ,, ,,	9·6	4·0	4·6	4·4				
	7·3	1·5	8·1	3·3			24 hr.	−
6. ,, ,,	12·3		5·3					
	11·0	4·0	6·1	1·9			36 hr.	+
7. Sheehan's syndrome	..	..	..	3·2	25·1* (48 hr.)		24 hr.	−

*T = 2·4 (normal 2·8–17).

insulin. The response of fat is, however, more variable than that of muscle, and this may limit the value of the fat response for insulin assay. The sensitive response of fat to insulin, and the bulk of this tissue, suggest that fat is one of the important sites of insulin action in the body.

Albumin inhibits the insulin response of muscle but not the insulin effect on fat. The differing effects of albumin on these two tissues may result from differences in glucose metabolism in fat and muscle. In muscle, a larger proportion of the glucose is converted to glycogen, and breakdown is almost entirely by the glycolytic pathway. In fat, approximately equal amounts of glucose are metabolised by the glycolytic and pentose-phosphate pathways, and only a small proportion is converted to glycogen. The albumin fraction may affect some stage of the process in muscle without interfering with metabolic pathways of glucose operative in fat.

The absence of albumin antagonism in fat has some importance in the design of insulin assays. Randle (1954) showed that fourfold dilution of human plasma resulted in no loss of insulin activity, measured by the diaphragm technique. This is probably due to the inactivation of insulin antagonists, among them the albumin antagonist, by dilution. Using a tissue such as fat which is not influenced by albumin, the more satisfactory 4-point design may be possible for serum-insulin assays.

Recent studies of the serum-insulin levels of 7 young untreated, ketotic diabetic patients (Steinke et al. 1961) are in line with our findings. By the diaphragm method, the insulin activity of these diabetics was half that of normal controls; but with epididymal fat, the diabetics showed insulin levels 50% above normal. Steinke and his colleagues suggest that an increased serum-insulin concentration in early juvenile diabetes may be ineffective with regard to muscle because of serum antagonists. Our evidence of the differing effects of albumin on muscle and fat may explain these results. Albumin from our 1 diabetic patient inhibited the muscle response to insulin slightly, and this was unaffected by hypophysectomy.

Unlike Vallance-Owen et al. (1958), we have found that inhibition of the diaphragm response by albumin persists after pituitary ablation. We believe this to be a non-specific effect of the albumin fraction, unrelated to the pituitary.

Summary

Albumin fractions of human sera inhibit glucose uptake of isolated rat diaphragm in response to insulin. The response of epididymal fat is not affected by albumin. This albumin antagonist is not dependent on the pituitary.

We are very grateful to Dr. Arthur Willcox, Dr. John Nabarro, and Miss Alison Cameron for encouragement and help. We thank the clinical research committee of the Middlesex Hospital Medical School for research facilities. One of us (C. L.) received a personal grant from the Medical Research Council, which is gratefully acknowledged. Recrystallised insulin was kindly supplied by Dr. E. V. B. Morton, of Boots Pure Drug Company Ltd.

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AN INSULIN ANTAGONIST ASSOCIATED WITH PLASMA-ALBUMIN

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WHEN insulin was added in vitro to the plasma from normal human subjects, there was no detectable insulin antagonism (Vallance-Owen and Hurlock 1954). Later, however, it was found that the plasma from untreated or uncontrolled insulin-requiring diabetic patients possessed this property, demonstrated by inhibition of the activity of insulin added in vitro, upon the glucose uptake of rat diaphragm (Vallance-Owen et al. 1955). Subsequent experiments have shown that this antagonistic activity to insulin resides in the albumin fraction of the plasma proteins (Vallance-Owen et al. 1958a). The same workers also found that a substance antagonistic to insulin was present in the albumin fraction of plasma from normal subjects, though this fraction was less active than that from the plasma of the diabetic patients.

No antagonism could be detected in albumin from hypophysectomised subjects. Also, albumin prepared from the plasma of insulin-requiring diabetics or normal subjects, when applied to a cellulose column, could be eluted completely free of antagonistic activity, though remaining electrophoretically unchanged (Vallance-Owen et al. 1958b).

Together, these findings suggest that the anti-insulin activity of the albumin fraction from normal subjects and from diabetic patients is not due to albumin itself but to a substance associated with it. In view of the increased antagonistic activity of the diabetic plasma protein, this substance is probably present in larger amounts on diabetic albumin than on normal albumin.

The results of hypophysectomy indicate that the antagonistic activity is related, possibly indirectly, to the pituitary gland. This gland may not be solely responsible, however, as is suggested from studies on experimental diabetes in animals. Thus, in depancreatised cats, insulin antagonism in their plasma depends on the presence of both pituitary gland and adrenocortical steroids (Vallance-Owen and Lukens 1957).

The objects of the investigation reported here were (1) to see if the observations made in laboratory animals were also true in man; and (2) to try to ascertain the nature of the active compound.

Material and Methods

Plasma

Venous blood was withdrawn into a heparinised syringe from non-fasting normal cats, and two totally adrenalectomised patients. One patient had adrenalectomy for carcinomatosis, the other for Cushing's syndrome, and neither had received any cortisone therapy for at least 50 hours before the blood samples were withdrawn. The plasma was quickly separated by centrifugation.

Preparation of Albumin

Albumin has been prepared from adrenalectomised human fluid plasma, reconstituted normal freeze-dried plasma, and from normal cat plasma by the method of Debro et al. (1957) as modified by Vallance-Owen et al. (1958a).

An equal volume of 10% trichloroacetic acid (T.C.A.) was

TABLE I—EFFECT OF HUMAN ALBUMIN AND SUPERNATANT FROM HEAT-COAGULATED HUMAN ALBUMIN ON BASAL UPTAKE *

Mean glucose uptake above basal level* ± S.E.M. (mg. glucose per 100 ml. per 10 mg. rat diaphragm)	
4% albumin in buffer alone	Supernatant from heat-coagulated albumin (≡11%)
−0·42 ± 0·86 (5)	0·30 ± 0·92 (5)

S.E.M. = standard error of mean.
* Amount of glucose taken up by diaphragm when no insulin is present in incubation medium.
Number of individual observations in parentheses.

added to the plasma or reconstituted freeze-dried plasma, the supernatant after centrifugation was discarded, and the precipitate washed with 5% T.C.A. The precipitate was then suspended in 1% T.C.A./96% aqueous ethanol in a volume equivalent to three times the original volume of plasma. After centrifugation the extract was dialysed for 72 hours and freeze-dried. As previously found (Vallance-Owen et al. 1958a), paper-electrophoresis of these albumin fractions failed to reveal any significant amounts of other plasma-proteins.

Detection of Insulin Antagonism

Insulin antagonism was determined by the rat-diaphragm assay procedure previously described (Vallance-Owen and Hurlock 1954, Vallance-Owen et al. 1955).

TABLE II—ALBUMIN FROM NORMAL CATS

Fraction	Mean glucose uptake above basal level ± S.E.M. (mg. glucose per 100 ml. per 10 mg. rat diaphragm)		
	Buffer + 1000 micro-units per ml. insulin	Fraction in buffer + 1000 micro-units per ml. insulin	Fraction in buffer alone
Cat albumin 4%	15·08 ± 0·99 (4)	8·62 ± 1·12 (4)	0·37 ± 0·75 (3)

Number of individual observations in parentheses.

The freeze-dried fractions obtained were dissolved in buffer solution (Gey and Gey 1936) containing glucose 0·3% w/v, and any insoluble matter removed by centrifugation. Insulin was added to the buffer alone and to the buffer with the dissolved fraction to make a final concentration of 1000 micro-units per ml.

In any one experiment the glucose uptake of the diaphragm was determined in: (a) buffer alone (basal uptake); (b) buffer plus added insulin (standard); (c) buffer with dissolved fraction plus added insulin. A few experiments, however, were carried out with buffer with dissolved fraction without added insulin for direct comparison with (a)—i.e., buffer alone. The uptake

TABLE III—A. ALBUMIN FROM ADRENALECTOMISED PATIENTS, NOT RECEIVING CORTISONE

Fraction	Mean glucose uptake above basal level ± S.E.M. (mg. glucose per 100 ml. per 10 mg. rat diaphragm)	
	Buffer + 1000 micro-units per ml. insulin	Fraction in buffer + 1000 micro-units per ml. insulin
Adrex. albumin 4%	12·50 ± 0·85 (4)	12·34 ± 0·98 (4)
Normal albumin † (3·5–5·5%)	11·43 ± 0·62 (6)	0·50 ± 0·48 (6)

† Vallance-Owen et al. (1958a).
Adrex. albumin = albumin from adrenalectomised patients.

B. ALBUMIN FROM ONE OF THE ADRENALECTOMISED PATIENTS (TABLE IIIA) RESTABILISED WITH CORTISONE

Fraction	Mean glucose uptake above basal level ± S.E.M. (mg. glucose per 100 ml. per 10 mg. rat diaphragm)	
	Buffer + 1000 micro-units per ml. insulin	Fraction in buffer + 1000 micro-units per ml. insulin
Adrex. albumin 4%	16·38 ± 0·54 (3)	6·03 ± 0·61 (3)

Number of individual observations in parentheses.

was ordinarily measured three times in 2 ml. aliquots of each solution, diaphragms from three different rats being used, and the results expressed in milligrammes of glucose per 100 ml. solution per 10 mg. dry weight of diaphragm over the 90-minute incubation period.

Attempted Separation of Antagonist from Albumin

Heat coagulation.—Human albumin (1 g.) in 100 ml. water was adjusted to pH 5·5 and boiled for 5 minutes. The heat-coagulated protein was separated from the supernatant liquid by centrifuging; was freeze-dried, and then dissolved in 9 ml. buffer. Half of the supernatant was dialysed in 'Visking' tubing (2·3 cm. flat diameter) against distilled water for approxi-

TABLE IV—INSULIN ANTAGONISM OF FRACTIONS FROM HEAT-COAGULATED ALBUMIN

Mean glucose uptake above basal level ± S.E.M. (mg. glucose per 100 ml. per 10 mg. rat diaphragm)			
Buffer + insulin ‡	Coagulated protein + insulin ‡	Supernatant liquid + insulin ‡	Dialysed supernatant + insulin ‡
18·91 ± 0·54 (9)	17·69 ± 0·81 (5)	11·16 ± 0·86 (5)	19·05 ± 0·72 (5)

Number of individual observations in parentheses.
‡ Insulin added to make a final concentration of 1000 micro-units per ml.

mately 4 days and the dialysate collected and evaporated to dryness in vacuo. Dialysed and undialysed supernatants, containing about 5% total solids, were freeze-dried and in each instance dissolved in 9 ml. buffer for assay.

Alcoholic extraction.—Albumin (1 g.) was refluxed with 100 ml. ethanol for 2 hours. The separated denatured protein was resuspended in water, alcohol removed as far as possible by vacuum distillation, and the residue freeze-dried and dissolved in 9 ml. The alcohol extract was evaporated to dryness in vacuo and the lipid-like residue suspended in 9 ml. buffer by warming in a closed vessel.

Extraction of long-chain fatty acids.—Albumin (0·8 g.) was twice extracted in the cold with 100 ml. of 5% glacial acetic

TABLE V—EXTRACTION OF ACTIVE ALBUMIN WITH HOT ETHANOL, ISO-OCTANE/ACETIC ACID, AND CHLOROFORM

Treatment	Mean glucose uptake above basal level ± S.E.M. (mg. glucose per 100 ml. per 10 mg. rat diaphragm)		
	Buffer + insulin ‡	Residual protein + insulin ‡	Organic extract + insulin ‡
Ethanolic refluxing (1 g. albumin)	17·60 ± 1·44 (3)	19·70 ± 2·02 (3)	15·27 ± 2·28 (3)
Iso-octane/acetic acid extraction (0·8 g. albumin)	15·28 ± 1·08 (5)	11·97 ± 1·63 (3)	15·87 ± 0·99 (3)
Chloroform extraction of aqueous solution (0·8 g. albumin)	13·90 ± 0·54 (11)	12·26 ± 0·79 (7)	13·04 ± 0·46 (5)

Number of individual observations in parentheses.

acid in *iso*-octane (Goodman 1957). The decanted organic solvent extracts were evaporated to dryness in vacuo, ensuring complete removal of acid, and the resultant fatty residue warmed to effect suspension in 9 ml. buffer. The protein was dissolved in water, dialysed free of the organic liquids, and freeze-dried.

Chloroform extraction.—Albumin (0·75 g.) in 75 ml. water was extracted three times with 100 ml. chloroform at room temperature. The combined organic phases, separated from the aqueous phase and interfacial precipitate by centrifuging, were evaporated and the residue warmed with 9 ml. buffer. After dialysing free of chloroform (7 days), the aqueous protein solution was freeze-dried and then taken up in 9 ml. buffer for assay.

Results

The series of experiments recorded horizontally in the tables II–V are units in themselves and show whether the material studied in each case is antagonistic to insulin. The fact that the sensitivity of the diaphragms to insulin varies occasionally is of no consequence. The variation

of the responses for each horizontal series can be seen from the standard errors of the mean given in the tables.

Table I shows that neither 4% human albumin nor the supernatant from heat-coagulated human albumin (equivalent to 11%) reduces the basal uptake of the diaphragms when no insulin is added to the incubation medium. In each case the figures do not differ significantly from zero.

Table II shows that normal cat albumin at 4% concentration exhibits significant and considerable antagonism to insulin. This activity is less than that obtained with a similar concentration of normal human albumin (table IIIA).

Table IIIA records the results in the two totally adrenalectomised patients in whom cortisone therapy had been discontinued for at least 50 hours. The plasma-albumin from these patients, tested twice in each case, had no demonstrable antagonistic activity to insulin.

Subsequently, the plasma-albumin from one of these patients was tested three times after her stabilisation with cortisone. Then, as with albumin from normal subjects, this fraction showed highly significant insulin antagonism (table IIIB).

The results of attempts to separate the active antagonistic principle from albumin are shown in tables IV and V. After heat coagulation, the denatured protein shows no antagonism, whereas its corresponding supernatant fluid shows this property, which is lost on dialysis (table IV). There is clearly some inactivation of the antagonist by heat.

In all these experiments, antagonistic activity was found in the dialysate. It has now been shown, however, that visking tubing, when used for dialysis over long periods, itself gives rise to a substance which antagonises insulin and which appears in the dialysate, contaminating the true active principle (Lilley and Vallance-Owen 1961). No antagonistic activity has been found, however, in corresponding retentate controls.

After refluxing with ethanol, neither the denatured protein nor the alcoholic lipid extract exhibited any antagonistic activity. No dialysis was involved here and the procedure therefore appears to result in complete loss of antagonism.

Goodman's *iso*-octane/acetic-acid extraction method does not lead to concentration of the antagonist in the fatty-acid fraction; also chloroform fails to extract antagonistic activity from an albumin solution (table V).

Though in the last two extraction procedures the residual protein also exhibited no antagonism, it had to be extensively dialysed before testing, in order to ensure complete removal of the reagents. Thus it is uncertain whether this loss results from the action of the organic solvents or from passage of the active principle into the dialysate. This point has not yet been elucidated, because of the non-specific antagonistic substance associated with visking membrane.

Summary and Conclusions

Albumin from normal subjects or from normal cats, in physiological concentration, does not depress the glucose uptake of muscle tissue.

The plasma-albumin fraction of normal cats antagonises insulin, though it is less active than the corresponding fraction from normal human subjects.

Albumin from the plasma of two patients in whom bilateral adrenalectomy was performed and in whom cortisone therapy was discontinued for at least 50 hours was non-antagonistic to insulin. In one of these patients, subsequently stabilised with cortisone, insulin antagonism was found in the plasma-albumin fraction. These observations suggest that, as with plasma from depancreatised cats, the insulin antagonism associated with normal human albumin depends on the presence of adrenocortical steroids as well as the pituitary gland.

The insulin antagonist can be separated from normal human albumin and rendered dialysable by heat coagulation of an albumin solution. There appears to be some inactivation of the antagonist by heat.

Removal of lipid material from albumin by refluxing with ethanol results in complete loss of antagonism, neither the extract nor the residual protein containing any activity.

Extraction of long-chain fatty acids with a mixture of *iso*-octane and acetic acid does not lead to concentration of the antagonist in this fatty-acid fraction.

In addition, chloroform fails to extract antagonistic activity from an albumin solution.

These last four observations suggest that the antagonist is of low molecular weight, and is unlikely to be a free lipid, fatty acid, or steroid-type compound. Thus, the antagonist may be a polypeptide or a simple carbohydrate, but lability to organic liquids under certain conditions supports a polypeptide structure.

Experiments are now being designed to isolate the active principle from albumin by various chromotographic methods.

We should like to thank Miss Margaret Jackson for valuable technical assistance; Prof. Russell Fraser and Prof. R. B. Hunter for allowing us to study patients under their care; the British Diabetic Association and the British Insulin Manufacturers for research grants; and Boots Pure Drug Company for supplies of recrystallised insulin.

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Preliminary Communication

INSULIN ANTAGONISM IN THE PLASMA OF OBESE DIABETICS AND PREDIABETICS

EARLIER studies on untreated or uncontrolled insulin-requiring diabetic patients showed that their plasma had no insulin activity and effectively inhibited the activity of insulin added in vitro,[1] and that this antagonistic activity resides in the albumin fraction of the plasma protein.[2] The whole plasma from normal subjects [3] and from obese diabetic patients [1] possesses insulin activity and has no measurable insulin antagonism. Nevertheless, when normal plasma is broken down into its various constituents, insulin antagonism can be found in the albumin fraction,[2] though this fraction is less active than that prepared from the plasma of the insulin-requiring diabetic patients. In concentrations of 3·5–5·5% both diabetic and normal albumin completely inhibited the

1. Vallance-Owen, J., Hurlock, B., Please, N. W. *Lancet*, 1955, ii, 583.
2. Vallance-Owen, J., Dennes, E., Campbell, P. N. *ibid.* 1958, ii, 336.
3. Vallance-Owen, J., Hurlock, B. *ibid.* 1954, i, 68.

effect of 1000 micro-units per ml. of insulin added in vitro. At 1·25%, however, diabetic albumin is still highly antagonistic, whereas normal albumin is now inactive [2] (see table).

In each instance, the antagonism is due not to the albumin itself but to a substance associated with it. In view of the increased antagonistic activity of the diabetic plasma protein, this substance is presumably present in larger amounts on diabetic albumin than on normal albumin. The antagonistic effect of albumin appears to be completely masked in whole normal plasma by the production of adequate amounts of insulin by the normal pancreas, but in laboratory animals it can be revealed when the pancreas is removed.[4]

INSULIN ANTAGONISM OF PLASMA-ALBUMIN FROM OBESE DIABETICS AND PREDIABETICS

Fraction	Mean glucose uptake above basal level * ±S.E.M. (mg. glucose per 100 ml. per 10 mg. rat diaphragm)	
	Buffer + 1000 micro-units per ml. insulin	Fraction in buffer + 1000 micro-units per ml. insulin
Obese diabetic albumin 1·25%	13·44 ± 0·62 (5)	4·43 ± 1·34 (5)
Prediabetic albumin 1·25%	15·28 ± 0·77 (6)	6·05 ± 0·99 (6)
Normal albumin[2] 1·25%	11·32 ± 0·74 (4)	11·17 ± 0·89 (4)
Insulin-requiring diabetic albumin [2] 1·25%	12·32 ± 1·05 (4)	3·55 ± 0·67 (4)

* Amount of glucose taken up by diaphragm when no insulin is added to medium.
No. of observations in parentheses.

It was of interest, therefore, to prepare albumin from the plasma of obese diabetic patients and from prediabetics. " Prediabetes " connotes " the state of a person during the period before he or she becomes plainly and clinically diabetic, in which, however, there is a latent abnormality which may show itself under certain specific conditions ".[5]

MATERIALS AND METHODS

Five obese diabetic patients, aged 54–73, were studied (four women and one man); all had severe glycosuria but no ketonuria, and had either fasting blood-sugar levels above 150 mg. per 100 ml. or typical diabetic glucose-tolerance tests.

The six prediabetics investigated were females ranging from 6 to 41 years old; all had a family history of diabetes; normal glucose tolerance or only marginal impairment (in two, fasting level achieved by $2^1/_2$ hours); but who had had typical diabetic curves during pregnancy, infection, or after cortisone or prednisolone orally. One patient has had 2 stillbirths; one needed insulin during the latter part of pregnancy, which was complicated by toxæmia necessitating a cæsarean section. Another presented with hypoglycæmia and was later found to have a diabetic curve after prednisolone.

Blood was withdrawn in the non-fasting state into a heparinised syringe, and the plasma quickly separated by centrifugation. The method of preparing albumin from plasma and the technique of the isolated rat diaphragm used for measuring insulin antagonism has been detailed elsewhere.[1–3 6]

RESULTS AND DISCUSSION

The albumin was tested in each case at 1·25%, and as the individual results for each group were essentially similar they have been taken together, and are recorded in the table. At a concentration of 1·25% both the prediabetic and the obese diabetic albumins were antagonistic to insulin, to the same extent as albumin prepared from the plasma of insulin-requiring diabetics, and to a considerably greater extent than that of normal albumin, which is inactive at this concentration. Thus far, no increased antagonism has been found with plasma-albumin from obese, but otherwise normal, persons. Experiments are in hand to test the degree of antagonism in the albumin from the plasma of diabetic patients suffering from hæmochromatosis or who have had total pancreatectomy.

If these observations are confirmed by further studies, they suggest that the primary abnormality in essential diabetes mellitus is increased antagonism to insulin, which the " diabetic " subject presumably inherits. The type and time of onset of the diabetic state then would depend on the degree of antagonism and on the resilience of the β-cells of the pancreas. The antagonism is apparently mediated through the pituitary-adrenal system; therefore it is reasonable to suppose that this antagonism will be further increased under certain conditions, notably the growth spurt, pregnancy, infection, or mental stress—times and situations which are known to precipitate the diabetic state in susceptible people. Again, there is well-documented evidence that the mean size of the islets of acute diabetics over the age of 5 is greater than that of controls, but the weight of the islet tissue and size of the islets in both acute and chronic diabetics diminish in proportion to the duration of the disease.[7] Recent observations that untreated juvenile diabetics possess insulin in considerable quantity,[8] and prediabetics have more circulating insulin than normal,[9] are in keeping with this concept.

Thus, provided the diabetic state is not manifested early in life by a relative breakdown in insulin production, more insulin is presumably being produced to counteract the excess antagonism. There is now some evidence that this antagonism does not affect insulin action on adipose tissue.[10] Therefore, it is tempting to suggest that obese diabetics become obese *because* they are diabetic; after the age of 40, newly diagnosed diabetics are, on average, appreciably heavier than normal people. The mean excess of weight is almost 12% in each sex.[11]

Provided albumin can pass through the placenta from the maternal to the fœtal circulation—there is some evidence that this may occur [12]—then the hypertrophied islet of the stillborn fœtus of a prediabetic mother can be explained, as can its fat flabby appearance.

We should like to thank Miss Margaret Jackson for valuable technical assistance; Prof. D. V. Hubble and Dr. G. O. Richardson for allowing us to study patients under their care; the British Diabetic Association and the British Insulin Manufacturers for research grants; and Boots Pure Drug Co. for supplies of recrystallised insulin.

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4. Vallance-Owen, J., Lukens, F. D. W. *Endocrinology*, 1957, **60**, 625.
5. Jackson, W. P. U. *Post Grad. med. J.* 1959, **35**, 287.
6. Vallance-Owen, J., Lilley, M. D. *Lancet*, April 15, 1961, p. 804.
7. Maclean, N., Ogilvie, R. F. *Diabetes*, 1959, **8**, 83.
8. Steinke, J., Taylor, K. W., Renold, A. E. *Lancet*, Jan. 7, 1961, p. 30.
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10. Lowy, C., Blanshard, G., Phear, D. *Lancet*, April 15, 1961, p. 802.
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Reviews of Books

Urban Redevelopment and Social Change

A Study of Social Conditions in Central Liverpool 1955–56. CHARLES VEREKER, JOHN BARRON MAYS, department of social science, University of Liverpool. Liverpool: University Press. Social Research Series. 1961. Pp. 150. 25*s*.

THIS report, designed to provide background for a series on different aspects of the life of the area, deals with conditions in the Crown Street district of Liverpool, long past its best. It studies the social structure and family life of the district against the background of its economic and living conditions. 60% of the occupied heads of families worked in inner Liverpool. Good transport facilities and a preference for remaining near the place of employment restrained movement away to outlying areas. Local families tended to remain rooted to the district: 40% of those studied had brothers and sisters near at hand. 62% of the inhabitants of blocks of municipal flats were against moving, although their neighbours thought the flats were the least satisfactory accommodation in the district. Contacts with social organisations were few. Only 9% of the children under 15 took part in organised youth activities. Contacts with further education were slight; children attending grammar schools or technical schools represented less than 3% of the total school population in the district.

There is an inherent conflict between the physical and social demands present in the urban situation; there is need for more awareness of the assumptions made by other specialists in fields of inquiry shared by more than one discipline. It is not easy, when framing redevelopment policy, to balance conflicting claims; in a changing world some degree of sacrifice may be necessary from both planners and planned. Balance requires that two different and equally desirable aims should be secured more or less simultaneously—the provision of adequate physical conditions, on the one hand, and the maintenance of social connectedness and family relationship, on the other. " To extend all our civic resources in the creation of new housing estates to the neglect of the deteriorated inner urban districts is to build up for the future further social problems which, if not worse, may at any rate prove to be as serious as those that were posed by the slums of the past ".

Gynæcological Urology

Compiler and editor: ABDEL FATTAH YOUSSEF, M.B., D.S., D.G.O., M.CH., F.I.C.S., lecturer in obstetrics and gynæcology, Cairo University. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960. Pp. 893. 180*s*.

THERE has been no comprehensive account of female urology since Everett's monograph appeared in the United States in 1947, and this book is designed to bring the subject up to date. Dr. Youssef has had the help of 31 contributors from eight countries.

The first section traces briefly the history of female urology from the early 19th century to the present. The second deals principally with the anatomy and physiology of the urinary tract, but something is said of the action of drugs upon the bladder. The ætiology, investigation, and management of bladder, urethral, and ureteral fistulæ are considered in the next section. Sphincter incontinence of urine is discussed in section four, and then follow a few chapters on urological diseases which may affect the genital tract—e.g., cystitis, calculi, and tumours of bladder and urethra. Section six deals with gynæcological conditions, such as prolapse, malignant disease, and infection, which may affect the renal tract. The last part of the book contains various topics hard to fit into any of the other sections—prevention and treatment of urinary-tract injuries in obstetrics and gynæcology, the operation of anterior pelvic exenteration, the artificial bladder, and oliguria and anuria in obstetrics and gynæcology.

With so many contributors it is hard, even with cross-references, to maintain a sense of continuity. The chapters appear rather as a series of short monographs, and it is unsatisfactory to find the ætiology, investigation, and management of some disorders dealt with in separate chapters by different authors. The text is authoritative but the illustrations, in general, are disappointing.

In editing an international volume Dr. Youssef has undertaken a formidable task. The importance of different subjects varies from one country to another. In some areas the need is for emphasis on the management of traumatic urinary fistulæ; post-radiation necrosis is a great problem in other areas. Where clinical standards are high and fistulæ uncommon, great interest centres on the prevention of chronic urinary infection after obstetric and gynæcological operations. Bilharziasis of the bladder (chapter 26) is of little interest to clinicians in Western Europe. In fact, gynæcological urology might be better presented on a national rather than an international basis.

Leitfaden der Gewebezüchtung

J. ŘEŘÁBEK and E. ŘEŘÁBEK. Jena: Gustav Fischer. 1960. Pp. 370. DM 64.90.

THOUGH Carrel published the first of his work on tissue culture in 1911, few books dealing specifically with this increasingly important subject have appeared. There have, however, been many articles in various scientific and medical journals—so many, in fact, that a two-volume bibliography was published in 1953.[1]

This valuable book covers all aspects of tissue culture from the planning of a suitable laboratory to minute details of the preparation of specimens for electron microscopy and autoradiography. Though the bulk of it is devoted to the culture of human and animal tissue-cells, a section deals with the special techniques for the cultivation of some of the more important viruses and protozoan parasites.

Though it is not easy reading, because a vast amount of information is compressed into just under 300 pages, the book covers the subject with the encyclopædic thoroughness of the best German texts. The bibliography alone occupies 45 pages and comprises about 1250 references to the world literature of tissue culture and allied subjects from 1900 to 1956. The photomicrographs, some of which are reproduced in colour, are admirable, but the German method of giving the magnification in terms of the power of the objective and of the eyepiece separately, though optically more precise, is unfamiliar to English eyes.

On the Causation of Varicose Veins

And their Prevention and Arrest by Natural Means. Surgeon Captain T. L. CLEAVE, M.R.C.P. Bristol: John Wright. 1960. Pp. 39. 7*s*. 6*d*.

HERE Captain Cleave restates and expands his argument [2] that Man and not Nature is to blame for varicose veins. He reasons skilfully that the single primary cause of varicose veins is delay in the passage of colonic contents and that the delay is due to a diet from which fibre has been removed. His new ideas and his critical attack on established doctrine are refreshing.

Recent Advances in Renal Disease (London: Pitman Medical Publishing Co. 1961. Pp. 254. 25*s*.).—Edited by Prof. M. D. Milne, this book records the proceedings of a conference held at the Royal College of Physicians of London last July. It deals with renal structure and function, acute renal failure and the artificial kidney, the nephrotic syndrome, pyelonephritis, metabolic aspects of renal disease, and the relation of the kidney to hypertension. The authors include the most renowned British names in this rapidly expanding subject, and they provide a convenient summary of present knowledge.

1. Murray, A. R., Kopech, G. A Bibliography of Research in Tissue Culture, 1884–1950. New York, 1953.
2. *Lancet*, 1959, ii, 172.

THE LANCET

LONDON 15 APRIL 1961

A New Concept of Diabetes

TEACHING about the pathogenesis of diabetes mellitus has changed several times in the past forty years. After the discovery of insulin in 1921, and its successful use in the treatment of diabetic patients, it was natural to assume that the cause of diabetes was a primary deficiency of insulin. This simple interpretation could no longer be fully accepted when it was found that numerous diabetics required much larger doses of insulin than patients who had a pancreatic-deficiency type of diabetes. Such large insulin requirements were explained by the presence of excessive quantities of insulin antagonists, such as adrenal glucocorticoids and pituitary growth hormone. In this way the exacerbation of diabetes by stress was explained by an adrenal mechanism, as was the insulin-resistant diabetes of Cushing's syndrome; whereas the diabetes associated with active acromegaly could be attributed to growth hormone. The increased pituitary activity at puberty and the increased hormonal secretions in pregnancy were held to account for the common increase in insulin requirement and peaks in the incidence of diabetes at these times. The development of techniques to measure insulin activity in plasma brought with them facilities to measure insulin antagonists in plasma. It is the results of such studies that now demand a reappraisal of our ideas about the cause of human diabetes.

Antagonists to insulin complicate the interpretation of bioassays of insulin-like activity; for RANDLE [1] showed that fourfold dilution of plasma did not reduce the insulin-like activity in his rat-diaphragm assay and supposed that this was due to a much more potent diluting-out effect on the antagonists than on the insulin. RANDLE has continued to work with such dilutions of plasma and has obtained considerably higher absolute figures of insulin-like activity per millilitre of plasma than other workers, such as VALLANCE-OWEN, who has used undiluted plasma.

BORNSTEIN and PARK [2] and HENDLEY et al.[3] studied the plasma of alloxan-diabetic rats and located insulin-antagonistic activity in a lipoprotein fraction. FIELD et al.[4] described insulin antagonism in the α_1-globulin fraction of the plasma proteins of severely ketotic patients; but it is the plasma albumin, rather than a lipoprotein or α_1-globulin, which appears to carry the insulin antagonism found in the blood of normal subjects, and in greater concentration in the blood of insulin-dependent diabetics even when they are not ketotic.[5]

The antagonistic action of the albumin in whole normal plasma was found to be balanced by some other substance, possibly insulin; for no antagonism occurred to the effects of insulin added in vitro, as measured by the rat-diaphragm technique.[6] By the same technique the plasma of hyperglycæmic diabetics, on the other hand, was found to inhibit the action of added insulin.[7] The factor causing the insulin antagonism could be separated from the albumin by passage through a column of cellulose in borate-phosphate buffer.[8] The factor appeared to depend on the pituitary, as shown by assays of plasma before and after surgical hypophysectomy.[8] On p. 804 VALLANCE-OWEN and LILLEY present data which indicate that the insulin antagonist associated with human plasma albumin depends also on adrenal cortical steroids. Thus VALLANCE-OWEN has produced evidence from human sources that parallels the results he obtained with LUKENS [9] on cats, in which pancreatectomy revealed the presence of insulin antagonists which depended on the integrity of the pituitary and adrenal glands.

When studies of plasma insulin activity and antagonism have employed the technique of ^{14}C glucose conversion to $^{14}CO_2$ by the rat epididymal-fat pad, the results have not agreed with those obtained by the rat-diaphragm bioassay. Thus STEINKE et al.[10] found that the serum insulin activity of seven young untreated ketotic diabetics was approximately half that of normal controls using the diaphragm method and 50% above normal using the epididymal-fat pad. The same type of discrepancy between the results of these two methods is reported by LOWY, BLANSHARD, and PHEAR in our present issue, and these workers could not confirm in one diabetic VALLANCE-OWEN's finding that the albumin-borne insulin antagonist depends on an intact pituitary. It may be concluded that the antagonist affects the action of insulin on the diaphragm but not significantly on the fat pad, possibly because the metabolic path of glucose differs considerably in these two tissues. The results of fat-pad studies indicate that the insulin activity of the blood of juvenile diabetics early in the course of their disease is above normal, and that the cause of the diabetes is probably the high level of insulin antagonists revealed by the diaphragm technique. VALLANCE-OWEN and LILLEY describe on p. 806 unusually high levels of insulin antagonism in the plasma of both obese diabetics and prediabetics, although this was not found in obese non-diabetic subjects. RANDLE [11] has found abnormally large amounts of plasma insulin in the blood of prediabetics.

From this recent work new hypotheses can be constructed which integrate aspects of diabetes that have been ill understood hitherto; and they will greatly stimulate further investigation. It may be supposed that the primary cause of both juvenile-onset and maturity-onset human diabetes is an abnormally high level of

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7. Vallance-Owen, J., Please, N. W. *ibid.* 1955, ii, 583.
8. Vallance-Owen, J., Dennes, E., Campbell, P. N. *ibid.* 1958, ii, 696.
9. Vallance-Owen, J., Lukens, F. D. W. *Endocrinology*, 1957, **60**, 625.
10. Steinke, J., Taylor, K. W., Renold, A. E. *Lancet*, 1961, i, 30.
11. Randle, P. J. Personal communication to Vallance-Owen and Lilley (p. 806).

insulin antagonists bound to plasma albumin. These antagonists, which are dialysable and possibly polypeptide in nature, appear to depend on the pituitary and adrenal glands, and would be expected therefore to vary with the activity of these glands. As the insulin antagonism occurs in muscle but not appreciably in fat, the high levels of plasma insulin found in prediabetes and early diabetes may actually favour the growth of adipose tissue—in other words the obesity so commonly found in newly diagnosed diabetics aged 40 or more.[12] It is possible, too, that the high level of insulin antagonists in diabetic patients is responsible for the development of diabetic complications, which are so similar in kind in the two main contrasting clinical types of diabetic, the juvenile-onset ketosis-prone and the maturity-onset ketosis-resistant. In this way some explanation could be offered for the favourable effects of ablation of pituitary or adrenal function on the progress of diabetic complications. As VALLANCE-OWEN points out on p. 806, the transfer of insulin antagonist from the blood of a diabetic or prediabetic pregnant woman to that of the fœtus may explain the characteristic hyperplasia of the β-cells of the fœtal pancreas. Later in the course of diabetes, insulin deficiency supervenes in parallel with the decrease in the amounts of pancreatic islet tissue with the increasing duration of the disease.[14] The occurrence of diabetes would depend, therefore, on the inherited liability to form excessive amounts of insulin antagonist and on the resilience of the pancreatic β-cells in responding to this challenge. Future work on the nature of the albumin-borne insulin antagonist may prove to be basic to the further understanding of the pathogenesis of diabetes mellitus.

Anaerobic Cocci

ROSENBACH [14] recognised the existence of cocci for which anaerobic conditions were not only tolerable but essential, and VEILLON [15] was probably the first to succeed in growing such organisms in pure culture. In the late 1890s the possibilities of culturing anaerobic organisms aroused widespread interest among bacteriologists, and within a few years many types of strictly anaerobic cocci had been isolated from every conceivable type of septic condition. The pathological significance of these organisms was usually obscure, though several of the earliest bacteriologists believed that anaerobic streptococci were important in infections of the female genital tract.

It was, however, SCHOTTMÜLLER and his school in Germany who first gave a clear indication of the importance of anaerobic streptococci in this type of infection. In an extensive series of investigations between 1910 and 1928, SCHOTTMÜLLER produced convincing evidence that a strictly anaerobic gas-producing streptococcus, which he named *Streptococcus putridus*, was often present in the apparently healthy vagina but was also an extremely common cause of puerperal sepsis and sepsis following abortion.[16] Workers in this country and the U.S.A. belatedly recognised that SCHOTTMÜLLER's experience was not exceptional, and today many would agree with him that anaerobic streptococci are more important than β-hæmolytic streptococci as a cause of infection of the female genital tract.

Why is it, therefore, that in the routine reports from our clinical laboratories we so rarely hear of the isolation of an anaerobic streptococcus or any other type of anaerobic coccus? The reasons are not far to seek: first, the colonies of anaerobic cocci have no distinctive features by which they can be recognised, and their discovery calls for a tedious trial-and-error process of sampling and testing; and secondly, when they are found, their gram reaction, morphology, and biochemical properties depend largely on the conditions of culture, and it is sometimes difficult to decide such seemingly simple questions as whether the organism is gram-negative or gram-positive and whether it is a streptococcus or a staphylococcus. The bacteriologist engaged in routine work wisely fails to find these organisms and rests secure in the knowledge that most of them are very sensitive to the commonly used antibiotics.

There are, however, a few bacteriologists who have made the anaerobic cocci their special hobby. In this country much of our new knowledge of anaerobic cocci is due to the work of HARE and his colleagues.[17 18] These workers have shown that by growing anaerobic cocci under defined conditions it is possible without undue difficulty to classify the majority into nine groups. Group 1, which corresponds to *Str. putridus* of SCHOTTMÜLLER, seems to be a homogeneous group of organisms, and there is good evidence that this organism is most commonly responsible for puerperal infections of the female genital tract. Attention has again been directed to this important group of organisms by HARE and POLUNIN,[19] who have investigated the cause of infertility in native women in British North Borneo. The number of women studied was small; but anaerobic cocci, and especially streptococci belonging to group 1 (*Str. putridus*), were clearly commoner in vaginal swabs from women from populations where infertility is a serious problem than in similar specimens from fertile populations living in the same area. POLUNIN [20] had already noted a very high prevalence of gynæcological abnormalities in the infertile group, and it is noteworthy that many of these abnormalities were of a kind which commonly follow infection with anaerobic streptococci. HARE and POLUNIN believe that infection following childbirth or abortion is a likely cause of the infertility of these women, and they provisionally suggest that organisms of group 1 may be important in this respect. Clearly, however, more work will have to be done before this can be proved. Indeed, the whole subject of anaerobic cocci still offers great scope for further research.

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Biological Aids to Respiration

THE oxygen cylinder, so familiar in medical practice, is equally familiar in aviation. As an airman ascends, the barometric pressure he experiences falls: at 18,000 feet, for example, the pressure is about half that at sea level; at 33,000 feet about a quarter; and at 52,000 feet about a tenth. The alveolar partial pressure of oxygen, upon which blood-oxygen saturation largely depends, falls even more steeply, because the water-vapour pressure, being a function of body-temperature, remains constant and the carbon-dioxide pressure changes very little; so a diminishing proportion of the total pressure is available to oxygen and the inert gases. The oxygen pressure is sufficient, up to 10,000 feet, for reasonable blood saturation, but sensitive functions such as night vision begin to deteriorate even at 5000 feet. Above 10,000 feet, symptoms of oxygen lack become more manifest and more dangerous as the aircraft climbs.

So long as flights did not exceed an altitude of 30,000 feet, it was possible to restore the alveolar oxygen pressure by a simple form of nitrogen replacement therapy. The early oxygen systems had this principle in common: oxygen, stored under pressure in steel bottles, was admitted to a tube or mask in quantities sufficient to enrich the breathing mixture, according to the altitude. Various devices regulated the enrichment. At first, when flights at great altitude were short, simplicity and reliability were more important than economy, and the gas was allowed to flow without interruption; but, as aviation developed, it became necessary to increase the duration of delivery without adding much to the gas capacity; and the inward flow was cut off during the expiration phase. During the 1939–45 war, systems of this sort became both flexible and reliable. Provided an aviator wore a well-fitting mask, he could rely on this simple method for full oxygenation up to 30,000 feet and for reasonable oxygenation up to 40,000 feet. If he wished to fly higher, he became anoxic though he was breathing pure oxygen; for the barometric pressure above 33,000 feet is insufficient to maintain the normal alveolar oxygen pressure without some form of supercharging.

Though all modern high-flying aircraft have pressure cabins, the crew must be protected in case of cabin failure at operational height. Various degrees of pulmonary supercharge are practicable: low positive pressure alone, higher pressure with external counter-pressure to the chest, and (the ultimate phase) high pressure with complete external counter-pressure—that is to say, a full pressure suit, which makes a man independent of the environmental pressure.

Most of the development work has been concerned with the means of regulating the flow and delivering it to the man. The range of equipment is considerable, from the mask which automatically presents itself for the airline passenger when cabin pressure falls, to the complex apparatus necessary to support an astronaut; but in twenty years storage methods have not changed much. The oxygen bottle is giving place to the liquid oxygen convertor, with some saving of weight and space. Chemical methods of generating oxygen, such as chlorate candles, have not seemed suitable for flight because the gas release is difficult to control. For all immediate purposes, whether in the atmosphere or beyond, liquid-oxygen storage offers ample gas capacity; but if Space is to be explored, and if voyages lasting a year or more are to be contemplated, it is necessary to find ways to reduce the weight which has to be sent aloft. Nor is the supply of oxygen the only respiratory problem: carbon dioxide, unless it is absorbed, soon reaches a toxic concentration in a small sealed cabin.

This is the background to the news that a scientist employed by the Boeing Airplane Company recently spent $26^1/_2$ hours, in a sealed tank, breathing oxygen produced by algæ.[1] These simple organisms, which are particularly rich in chlorophyll, use light energy to produce carbohydrate from carbon dioxide, putting out oxygen in the process. For some time attempts have been made to harness the chlorella algæ to maintain pure air in a closed space, but there have been many disappointments. The installation is bulky, since the algæ function best in a 1% suspension in water; the oxygen has to be pumped away from the tank; and light for photosynthesis must be provided when there is no natural illumination. On the other hand, if the algæ are supplied with urea, they multiply rapidly and may provide a protein supplement to what is likely to be a monotonous and not very palatable diet. The Surgeon General of the United States Air Force is reported to have said that the Boeing experiment " demonstrates the feasibility of supporting men on sustained space missions ". It seems, therefore, that another problem of space flight may have begun to yield to the determined efforts of the Americans; and the botanist may join his other biological colleagues as an important member of the space research team.

Annotations

OBSTETRICS AND THE HANDICAPPED CHILD

BETWEEN 1936 and 1948 perinatal mortality in this country fell dramatically: it seemed likely soon to approach an irreducible minimum. Unfortunately this aim has not been achieved; and the reasons were examined by Baird [2] in his Ingleby lectures.

Much could be achieved by improvement in the health and physique of mothers, by better organisation of the maternity services, and by a higher standard of obstetric practice. In the prevention of fœtal and neonatal deaths the need is not so much for further research as for the assiduous application of what is already known. In these circumstances it is understandable that research interest should turn from fœtal mortality towards morbidity; for the handicapped child is an important family and community problem. Possibly many different complications of pregnancy contribute to physical or mental defect, but about this published reports are contradictory. For

1. *Times*, March 16, 1961.
2. Baird, D. *Lancet*, 1960, ii, 557.

example, the effect of fœtal anoxia is still disputed [3–8], and the significance of prematurity has been affirmed and denied in a succession of papers.[9–11] Many disciplines meet in this area of investigation; and the difficulty of establishing adequate obstetric, pædiatric, social, genetic, and psychological data on a complete or representative population is formidable. Study of highly selected or incomplete populations or with inadequate definition of terms and criteria may account for some of the incongruity of the existing evidence. Two recent studies are of particular value; for they were made in Aberdeen where local arrangements favour the diagnosis and care of handicapped children, and where for the past twelve years detailed sociomedical records have been compiled for all births in the city.

Fraser and Wilks [8] have investigated the residual effects of neonatal asphyxia by examining 100 children who were known to have suffered delay in the onset of satisfactory respiration at birth. (Premature, twin, and illegitimate infants were excluded.) Asphyxia had been moderate in 60 cases and severe in 40; the reasons for the asphyxia were varied and in many cases multiple. Neurological examination at the age of $7\frac{1}{2}$ years revealed significant abnormality in very few; but minor disorders of personality, perception, and motor coordination were relatively common. The findings were checked against those in a control group.

Fairweather and Illsley [3] traced all mentally handicapped children born in Aberdeen in 1948 and still living there in 1958. Pregnancy and birth records were inspected for obstetric complications, and the mothers were questioned about their personal and family histories. From their detailed study of 66 cases Fairweather and Illsley concluded that recognisable obstetric complications made little direct contribution to the total volume of mental handicap. On the other hand the families from which these children came were characterised by a high frequency of marital and occupational instability, poor education, low intelligence, and ill-informed attitudes to health, nutrition, and child care. There were many instances of intermarriage between these backward families. To Fairweather and Illsley it seemed that these social and genetic factors were closely related to the development of mental handicap.

So far as the obstetric contribution to severe handicap is concerned, the situation is broadly reassuring; but both Fraser and Wilks and Fairweather and Illsley are cautious in their interpretation of what facts there are, and they rightly underline the need for long-term, well-planned, prospective studies. If it is confirmed that minor degrees of impairment commonly follow severe asphyxia, then the management of labour and methods of resuscitating the newborn will have to be carefully reviewed.

DUCT PAPILLOMA OF THE BREAST

A MIASMA of uncertainty has surrounded the natural history of duct papilloma. Does this condition become malignant, and if so how commonly? These are important questions, for on the answers rests the management of cases of discharge from the nipple. The problem really starts with identification, since both papillary duct carcinoma and benign papillary intraduct papilloma can present in the same way—with a serous or bloody discharge. Moreover it is not always easy to distinguish one from the other histologically.[1] Duct carcinoma is, however, relatively rare; Haagensen et al.[1] reported that only 1·3% of those presenting with a discharge from the nipple were shown to have carcinoma. Not unexpectedly (in view of the difficulty of diagnosis by orthodox histological means) exfoliative cytology has proved an uncertain guide.[1] Papanicolaou himself outlined the limitations of his techniques in relation to breast lesions; and, though he declared that examination of secretion smears was a fairly reliable aid in the diagnosis of papilloma, the evidence for this is slender.[2]

Donnelly [3] sought to classify nipple discharge and correlate it with the mammary lesion. Thus he wrote of " stagnation " and " hyperplastic " discharge, sanguineous discharge coming into the second of these two categories. But he pointed out that " nipple discharge may be the initial and sometimes the only symptom of a malignant breast lesion ", and, if this is so, no amount of categorisation will help with the individual case. Madalin et al.[4] undertook a detailed study of 100 breasts from 85 patients who had undergone simple mastectomy on account of discharge from the nipple. They sought to answer three questions: (1) what lesions were present; (2) whether there was any tendency to malignant change in intraduct papillomas; and (3) whether malignancy was present in a breast providing a discharge from the nipple. The first of these questions could not be answered concisely; for the second they could only state that they found no evidence of malignant change in any intraduct papilloma; as regards the last, they encountered 1 case of cancer—in a patient who had previously developed carcinoma in the other breast. They found that in cases of carcinoma without a palpable mass the prevalence of discharge was very low (less than 1 case per annum at the Mayo Clinic), and the discharge was almost always bloody. Accordingly, for discharge without a mass they recommend only excision of the offending duct, and not mastectomy.

Snyder and Chaffin [5] reviewed 107 cases of papillary disease followed for from one to thirty (average ten) years. In no case did a patient die of carcinoma of the breast when an infiltrating carcinoma had not been found at the original operation. But 28 additional cases could not be traced.

In an entirely pathological study Saphir and Parker [6] distinguished between fibrous, glandular, and transitional types of papilloma. They were in no doubt that the first two had no evil in them; they were less certain about the last. Hendrick [7] had no doubts: from his study of 208 cases, 92% of which were followed for from five to eighteen years, he felt sure that intraduct papilloma was benign and therefore recommended treatment similar to that suggested by the Mayo Clinic workers.[4] In contrast Kilgore et al.[8] declared that the chance of cancer being present in cases of bloody discharge without a palpable mass is 4–5%, and from their study of 190 patients they

3. Fairweather, D. V. I., Illsley, R. *Brit. J. prev. soc. Med.* 1960, **14**, 149.
4. Darke, R. A. *J. Pediat.* 1944, **24**, 148.
5. Illingworth, R. S. *Brit. med. J.* 1955, ii, 1.
6. Lilienfield, A. M., Pasamanick, B. *Amer. J. Obstet. Gynec.* 1955, **70**, 93.
7. Graham, F. K., Caldwell, B. M., Ernhart, C. B., Pennoyer, M. M., Hartmann, A. F. *J. Pediat.* 1957, **50**, 556.
8. Fraser, M. S., Wilks, J. *J. Obstet. Gynæc. Brit. Emp.* 1959, **66**, 748.
9. Alm, I. *Acta pædiat. Stockh.* 1953, **42**, suppl. 94.
10. Drillien, C. M., *Arch. Dis. Childh.* 1959, **34**, 37.
11. Douglas, J. W. B., *Brit. med. J.* 1960, i, 1008.

1. Haagensen, C. D., Stout, A. P., Phillips, J. S. *Ann. Surg.* 1951, **133**, 18.
2. Papanicolaou, G. N., Holmqvist, D. G., Bader, G. M., Falk, E. A. *Cancer*, 1958, **11**, 377.
3. Donnelly, B. A. *Ann. Surg.* 1950, **131**, 342.
4. Madalin, H. E., Clagett, O. T., McDonald, J. R. *ibid.* 1957, **146**, 751.
5. Snyder, W. H., Chaffin, L. *Arch. Surg.* 1955, **70**, 680.
6. Saphir, O., Parker, M. L. *Amer. J. Path.* 1940, **16**, 189.
7. Hendrick, J. W. *Surg. Gynec. Obstet.* 1957, **105**, 215.
8. Kilgore, A. R., Fleming, R., Ramos, M. M. *ibid.* 1953, **96**, 649.

concluded that papillary disease indicated an above-average risk of cancer developing.

Lately 125 patients from the New York Hospital have been reviewed.[9] In 8 carcinoma developed at or near the scar of a previous incision for removal of a duct papilloma. In 3 of these the original pathological diagnosis was changed on review of the section to carcinoma; in 2 there was disagreement on review; in 2 carcinoma developed at a site where all pathologists agreed that only papilloma lay before; and in 1 case papilloma recurred at the old site and carcinoma was found nearby. Moore et al. are cautious about what deductions, if any, should be drawn from these findings.

RESTITUTION OF INTERNAL CAROTID ARTERY

CEREBRAL angiography has confirmed that spontaneous occlusion of the internal carotid artery is an important cause of both catastrophic and insidious intracranial lesions. Occlusion may also be symptomless: it has been found in 2·9% of unselected necropsies.[10] Remedies that have been tried include anticoagulants,[11] stellate block or ganglionectomy,[12] and direct attack on the occluded portion of the artery.[13 14]

Direct surgical operation is not often beneficial. Thrombosis may have extended to the intracranial portion of the vessel, or the brain may have suffered irreversible damage —or it may already have recovered by reason of a good anastomotic circulation. Dramatic improvement after operation is rare; and a downward gush of blood, or evidence of patency at postoperative angiography, is often unaccompanied by clinical improvement.

Reviewing 40 cases, in 32 of which operation was undertaken, Edwards et al.[15] found that, alter natively to sudden catastrophe or gradual development of disability, the patient might have a series of episodes of transient blindness or weakness of an arm before a final severe attack: they termed this a " stuttering " onset. The cause of the occlusion was an atheromatous plaque or ring, multiple plaques, or complete thrombosis extending intracranially. The last two types were inoperable. A solitary plaque was removed or, if possible, treated by end-to-end anastomosis. Grafts were not so satisfactory. Edwards et al. conclude that the main value of operation is in prophylaxis, especially in cases with a " stuttering " onset as opposed to gradual progression.

Riishede et al.[16] found that 20% of 300 cases of cerebral apoplexy were caused by extracranial occlusion of the carotid system. 32 patients were operated on. 28 had hemiparesis, maximal in the arm; 2 more had paresis confined to the arm. Aphasia was present when the dominant hemisphere was affected, and homonymous hemianopia was noted in 7 out of 19 who could be tested. Half the patients were drowsy at the onset. 10 had had one previous attack, and 7 had had more than one. All the patients selected for this study were over 40 years of age. Only 2 had significant hypertension; 4 had severe cardiac disease (coronary occlusion in 3, and auricular fibrillation in 1). Angiography revealed that the lesions fell into three groups: (1) complete occlusion in the proximal 3 cm. of the internal carotid artery; (2) complete occlusion with a slow streak of dye progressing as far as the base of the skull; (3) partial occlusion. In most cases there was evidence of atherosclerotic changes in the other cranial arteries. Occlusion was by atheromatous plaque or plaques, with, in most cases, thrombotic masses completing the occlusion. In 8 cases there was no plaque and only thrombus. In the second group the occlusion was commonly in the intracranial portion only. Spurting back-flow was obtained only in cases of partial occlusion and in a few cases of recent complete occlusion (within the previous twenty-four hours); and in such cases the circulation was apparently restored. Where back-flow was not spurting the circulation did not apparently remain patent. All the other operations were unsuccessful. Of the group with complete occlusion, only 1 had normal postoperative angiograms and complete clinical recovery. Of the group with incomplete occlusion 2 out of 8 recovered clinically. In the others impaired circulation in the cerebral arteries or permanent infarct precluded complete recovery. Of 14 patients without back-flow 6 improved clinically in time.

In each of these series a bruit was found to be a useful but inconstant guide; palpation of the arteries in the neck or in the tonsillar region proved unreliable; and measurement of the ocular or retinal arterial pressure was of limited value. Riishede et al. rightly declare that compression of the opposite carotid artery to produce convulsions or unconsciousness is inadvisable as a diagnostic test.

Cases for which the usefulness of operation seems to be clearly established are those with " stuttering " onset in which permanent disability has not yet developed. For the others action depends on how fervently one upholds the principle that two patent, though diseased, arteries are better than one when the brain has already been deprived at least temporarily of one of them with or without a catastrophic result. The possibility of dislodging an embolus at operation will loom large in the minds of the cautious; and it cannot be said that the figures allay suspicions on this or other scores. Clearly, however, cases caught in the stage of incomplete occlusion and episodes of threatened apoplexy merit serious consideration of surgical treatment. The information we need now is how often after operation transient attacks cease, and for how long.

DEVICES FOR RESUSCITATION

EXPIRED-AIR respiratory resuscitation continues to arouse wide interest, particularly among first-aid organisations; for there is now ample evidence that it is superior,[1] in most circumstances, to manual methods, and that it can be taught to laymen.[2] In this country the Armed Forces, the lifesaving societies, and various other organisations are seriously considering its adoption, at least as a supplement to established methods.

The question whether any ancillary apparatus for expired-air resuscitation should be carried by first-aid workers is still undecided. Some hold that any method of first-aid in acute respiratory insufficiency must be capable of instant application anywhere. Therefore it should not require ancillary apparatus; and even the use of ancillary apparatus as an optional accessory should be discouraged, lest it give the impression that it cannot be dispensed with, and lest its unskilled use should harm the patient. Others believe that, by getting over the æsthetic objection to

9. Moore, S. W., Pearce, J., Ring, E. *ibid.* 1961, **112**, 153.
10. Hultquist, G. T. Über Thrombose und Embolie der Arteria Carotis. Stockholm, 1942.
11. Millikan, C. H., Siekert, R. G. *Proc. Mayo Clin.* 1955, **30**, 578.
12. Poppen, J. L., Baird, W. C. *Surg. Clin. N. Amer.* 1952, **32**, 781.
13. Strully, K. J., Hurwitt, W. S., Blankenberg, H. W. *J. Neurosurg.* 1953, **10**, 474.
14. Eastcott, H. H. G., Pickering, G. W., Rob, C. G. *Lancet*, 1954, ii, 994.
15. Edwards, C. H., Gordon, N. S., Rob, C. *Quart. J. Med.* 1960, **29**, 67.
16. Riishede, J., Ottosen, P., Søndergaard, T. *Danish med. Bull.* 1960, **7**, 185.

1. Gordon, A. S., Frye, C. W., Gittelson, L., Sadove, M. S., Beattie, E. J. *J. Amer. med. Ass.* 1958, **167**, 320.
2. Dobkin, A. B. *Lancet*, 1959, ii, 662.

applying the rescuer's mouth to that of the victim, the several devices (such as mouth tubes and double airways) which are now available will ensure that expired-air resuscitation is more readily and promptly performed. A recent article [3] depicts many of these devices, most of which are small enough to be carried in the pocket; and it gives a fuller description of a comparatively recent addition to them, the 'Venti-Breather', which has proved satisfactory on evaluation. It consists of a light polyvinyl face-mask, to which is attached a short breathing-tube containing a one-way valve and port for the victim's expiration, and a detachable mouthpiece. It is difficult to see how the use, or even the gross misuse, of this device could cause harm to the patient, and easy to see that it might do a great deal of good.

We hope that those responsible for shaping the policy of first-aid organisations will decide that the time has now come to consider the issue, at least on a pilot scale, of one or other of these devices.

TEACHING PSYCHIATRY

MANY voices from within and without the profession have lately been complaining of deficiencies in undergraduate education in psychiatry in this country, and of our failure to train doctors to meet the challenges of modern mental medicine. In the House of Commons last month the unfulfilled demand by Mr. Kenneth Robinson for a Royal Commission on medical teaching hinged on inadequacies in our psychiatric teaching compared with other countries. Certainly the results of the British Medical Students' Association inquiry [4] contrast sharply with the tremendous range of some American training.[5] Though the present wave of London undergraduate chairs in psychiatry is welcome and will do much to raise standards everywhere, it remains to be seen how far the older specialties will be willing to hand over a larger share of the curriculum and, if they do, what use will be made of it. It is doubtful whether any school in this country would yield the hundreds of hours given to psychiatry in some transatlantic and even oriental schools,[6 7] and even more doubtful whether many of our psychiatric departments would know what to do with all this time if they got it. Almost everyone agrees that psychiatric training should be expanded, but there is not nearly enough discussion about how to do it.

A World Health Organisation report [8] on this subject comes aptly therefore. It points to the importance of psychiatry to the medical training as a whole:

> "The medical student has received an education less and less likely to show him that the human being has to be considered in his entirety and not thought of only as the carrier of a series of organs and organ systems to be dealt with by specialists. The student has even less opportunity of becoming acquainted with the contribution of the social sciences (sociology, social psychology, social anthropology, and cultural anthropology) to the knowledge of man as a whole or to realize their importance for medical practice. Many leaders in the field of medicine complain of a "dehumanization" of medical practice and by implication medical teaching, and look for remedial measures . . . Under these circumstances the status of psychiatry has begun to change. Besides being regarded as a fully developed specialty, it is also considered a sort of leaven permeating medicine as a whole. In some places this evaluation goes so far as to attribute to psychiatry the role of the philosophical department of compartmentalized medicine. In other areas it is recognized that psychiatry may be more of a catalyst that would help specialists in other fields to bring the student to a better understanding of the human being as a whole."

But the report remarks that as schools vary in their "depersonalisation" and distortion of the doctor's fundamental role, so will the role of the psychiatrist vary also. In broad terms the student should learn to recognise the main forms of psychiatric disorder and the presence of psychiatrically important factors in diseases of the body. He should realise how his own attitude to patients and their families is significant to his success or failure as a physician; and he should be taught that a general practitioner needs to collaborate with others involved in the care of the patient and to become the main agent in the community of mental hygiene and psychiatric prevention. From the earliest days in the biological sciences of structure and function, emphasis should be laid on their relationship to behaviour and emotion; and psychology and sociology should be considered as basic as anatomy and physiology in the teaching of psychiatry, and should run parallel to them. As for psychotherapy, while the W.H.O. committee were sure the student should be taught the applications and expectations of present methods, they counsel against training him to conduct it systematically and against teaching much "depth" psychology or the detailed theories of different schools. The simple doctor/patient therapeutic relationship, however, and dynamic individual and group psychology, should be covered in some degree, though there was the risk that throwing light on the mechanisms of human conduct can sometimes disturb medical students.

Psychiatric epidemiology, cultural anthropology, and therapeutic communities were among other topics the committee included, and the limitations to our knowledge of classification and prevention were also very relevant. The various aspects of psychology (specified in the report) cover 40 hours minimum of teaching, and of sociology 20 hours minimum. Formal psychiatry adds at least a further 60 hours, and there should be 4 or more weeks' full-time clinical clerkship with both inpatients and outpatients.

Commenting that the teaching of child psychiatry by pædiatricians or of psychosomatic disease by physicians relieves the burden on the psychiatric department, the committee add that "In too many schools the professor of psychiatry is losing valuable time through having to overcome the prejudices which the students bring to the psychiatric lecture room and which, at least to a certain extent, have been created by the teaching they have received in other departments." They point to the particular benefits of the small discussion group, of taking part in research, and of psychiatric teaching about patients from other departments (as Professor Stengel regularly does in Sheffield). Final examinations and rotating internships should both include psychiatry. The efficacy of the entire staff's teaching techniques should be regularly reviewed. The committee are agreed that outside minimum requirements, each centre should develop in its own way according to local needs and the particular views of heads of departments.

Mr. V. B. GREEN-ARMYTAGE, visiting gynæcologist and obstetrician at Hammersmith Hospital and a former professor in the University of Calcutta, died on April 11.

3. Cross, A. S. *Med. Ann. D.C.* 1960, **29**, 657.
4. Report on the Teaching of Psychiatry and Psychological Medicine in British Medical Schools. British Medical Students' Association, 1958-59.
5. See *Lancet*, 1960, i, 1015.
6. American Psychiatric Association, Psychiatry and Medical Education: Report of the 1951 Conference on Psychiatric Education, Cornell University, Ithaca, N.Y., 1951. Washington, 1952.
7. Lin, Tsung-Yi. *Brit. med. J.* 1960, ii, 345.
8. The Undergraduate Teaching of Psychiatry and Mental Health Promotion: Ninth Report of Expert Committee on Mental Health. *World Hlth Org. Tech. Rep. Ser.* 1961, no. 208. Geneva. Pp. 36. 1*s.* 9*d.* Obtainable from H.M. Stationery Office, P.O. Box 569, London, S.E.1.

Needs and Beds

AN EXAMINATION OF THE NEED FOR HOSPITAL ADMISSION

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IT is widely believed that the number of hospital inpatients could be considerably reduced by improved outpatient and domiciliary services. Two recent reports have provided support for this view. Crombie and Cross (1959) examined case-notes and interviewed relatives of a sample of patients discharged from or dying in the medical wards of a Birmingham general hospital. They concluded that a quarter of them "had no diagnostic or therapeutic requirements at hospital level". Forsyth and Logan (1960) discussed with consultants the needs of patients in hospitals in Barrow-in-Furness; they estimated that a quarter of the males and two-fifths of the females in adult medical wards were "not, on clinical grounds alone, in need of in-patient care".

In the course of an investigation into the needs of hospital patients during the last quarter of 1958 and January, 1959, all Birmingham general, special, and chronic hospitals were visited. They included chest and pædiatric hospitals but not obstetric units. These visits provided an opportunity to assess the need for admission of all Birmingham patients in hospitals other than mental and mental-deficiency hospitals and obstetric units.

The appropriate hospital physician was asked to consider whether, on medical grounds alone, each patient required admission to hospital. His opinion was recorded on a card by a medically qualified investigator from the department of social medicine.

For patients whose admission was considered unavoidable, the medical reasons for admission were noted. For those whose admission was avoidable the social reasons for admission were investigated. This was done from data provided by patients and hospital staffs and without home visits.

The physicians also considered whether patients were, in view of their medical condition, suitable for discharge at the time of the survey, and if so the reasons why they had not left hospitals.

ARE PATIENTS ADMITTED UNNECESSARILY?

It was considered that there were insufficient medical grounds for admission of 204 (4·7%) of the 4274 patients in hospital. The corresponding proportions in general and special hospitals were 1·6% of 2936 patients and in chronic hospitals 11·8% of 1338 patients.

Table I shows the home circumstances at the time of admission of the 204 patients whose admission was not essential for medical reasons. (Home circumstances of some patients were unsatisfactory in more than one respect, so that numbers cannot be added.) In only 9 cases was the home satisfactory: these were patients admitted for miscellaneous reasons—e.g., "a good teaching case", a senile patient admitted to enable relatives to take a holiday, and a child with whooping-cough from a house in which there was a young infant. In all other cases a satisfactory home was not available. Approximately two-fifths had a home which was inadequately attended, even although domestic help may have been available. This means that the person or persons sharing the home were unable, by reason of age or the need to earn a living, to give the necessary intermediate attention.

The services needed by patients whose admission was not essential are given in table II. (As in table I the same patient may be entered in more than one column.) The common requirements were domestic service (by approximately three-quarters of patients), domiciliary nursing (by three-fifths), and domiciliary medical care (by two-fifths). For patients in general hospitals the dominant requirement was medical care; for those in chronic-sick hospitals it was domestic service and nursing.

At first sight it might appear that most of these deficiencies could be made good by augmented local services. But the possibility of preventing hospital admission turns not only on the availability of the services indicated in table II but also on the existence of a home

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TABLE I—HOME CIRCUMSTANCES OF PATIENTS WHO DID NOT REQUIRE ADMISSION ON MEDICAL GROUNDS

Type of hospital	Number of patients	Home circumstances					
		Satisfactory	Unsatisfactory				
			Living alone	Attendance inadequate	House overcrowded or unsatisfactory	No home or communal home	Other
General and special	46	7	7	14	9	5	8
Chronic	158	2	37	70	8	36	11
Both types	204 (100%)†	9 (4·4)	44 (21·6)	84 (41·2)	17 (8·3)	41 (20·1)	19 (9·3)

Home circumstances of 13 patients were unsatisfactory in more than one respect. Hence numbers cannot be added.
† In this and subsequent tables percentages are given in parenthesis.

TABLE II—SERVICES NEEDED BY PATIENTS WHO DID NOT REQUIRE ADMISSION ON MEDICAL GROUNDS

Type of hospital	Number of patients	Services needed					
		Outpatient investigation	Outpatient treatment	Domiciliary nursing	Domiciliary medical care	Domestic services	Other
General and special	46	3	3	18	37	19	5
Chronic	158	3	6	106	44	128	7
Both types	204 (100%)	6 (2·9)	9 (4·4)	124 (60·8)	81 (39·7)	147 (72·1)	12 (5·9)

121 patients required more than one type of service.

TABLE III—SERVICES NEEDED BY PATIENTS WHO REQUIRED ADMISSION ON MEDICAL GROUNDS

Type of hospital	Number of patients	Services needed					
		Investigation	Medical treatment	Surgical treatment	Nursing care	Other	Multiple
General and special	2890 (100%)	189 (6·5)	1394 (48·2)	1264 (43·7)	13 (0·5)	21 (0·7)	9 (0·3)
Chronic	1180 (100%)	30 (2·5)	634 (53·7)	81 (6·9)	426 (36·1)	5 (0·4)	4 (0·3)

with the ancillary help which relatives and friends might be expected to provide. For example, it was considered that even if there had been domestic help, nearly half of those requiring it would be without the complementary assistance which might make it possible to prevent admission.

It should perhaps be stressed that we are here concerned only with the physician's assessment of the patients' condition and needs at the time of admission. Of the 204 patients whose admission was considered unnecessary, 61 were thought to need hospital care at the time of the survey because since admission their condition had deteriorated or they had developed intercurrent illness.

TABLE IV—REASONS FOR RETENTION OF PATIENTS READY FOR DISCHARGE

Type of Hospital	Number of Patients	Reasons for retention		
		Social circumstances	Awaiting final review or arrival of relatives	Awaiting transfer
General & special	288 (100%)	82 (28·5)	179 (62·2)	27 (9·4)
Chronic	274 (100%)	256 (93·4)	17 (6·2)	1 (0·4)

Table III gives information about the 4070 patients whose admission was regarded as necessary. (In this table patients are classified according to the predominant reason for admission and the percentages can be added.) As would be expected, in general and special hospitals the common reasons for admission were medical or surgical treatment. Even in chronic-sick hospitals these two requirements accounted for three-fifths of the admissions, and nursing care (independently of medical treatment) for only about one-third.

ARE PATIENTS RETAINED UNNECESSARILY?

The physicians held that from a medical viewpoint 562 patients (13·1% of 4274) were ready for discharge at the time of the survey. The reasons for failure to discharge are given in table IV. Approximately three-fifths were delayed for social reasons; a third were awaiting final review or arrival of friends; and a small number were to be transferred to another institution. As would be expected, the proportions in each group are very different in general and chronic-sick hospitals.

Table V examines the home circumstances of the 338 patients whose discharge was prohibited on social grounds, and table VI shows the services they required. The pattern is similar to that already noted for patients whose admission was avoidable (tables I and II): most of them either had no home or the attendance available was inadequate; and the services most often required were medical treatment (patients in general hospitals) and nursing care and domestic service (patients in chronic-sick hospitals). It is clear that the possibility of discharge, as of avoidance of admission, turns upon home circumstances as well as upon improved domiciliary services.

Of the 204 patients who need not have been admitted on medical grounds, 61 (mainly elderly patients) had deteriorated since admission and therefore could not be discharged. The release of the remaining 143 patients was delayed solely for social reasons. (They are of course included in the 338 patients considered in tables V and VI.) Their need for domestic service and adequate attendance at home was as great as when they were admitted; but the proportion with no home of their own had risen from 22% to 30%.

28 patients were awaiting transfer to other institutions (table IV): 11 to chronic-sick wards; 7 to convalescent homes; 3 to the country branch of the parent hospital; 2 to a sanatorium; 1 to an open-air school; 1 to Roehampton; and 3 to mental-deficiency hospitals.

Patients awaiting final review or arrival of relatives require no further comment.

There were 3712 patients (86·9% of 4274) whose retention in hospital was thought essential on medical grounds. The proportion in general and special hospitals was 90·1% and in chronic hospitals 79·6%.

TABLE V—HOME CIRCUMSTANCES OF PATIENTS WHOSE DISCHARGE WAS DELAYED FOR SOCIAL REASONS

Type of hospital	Number of patients	Home circumstances					
		Satisfactory	Unsatisfactory				
			Living alone	Attendance inadequate	House overcrowded or unsatisfactory	No home or communal home	Other
General and special	82	9	9	29	19	18	13
Chronic	256	5	45	88	17	106	12
Both types	338 (100%)	14 (4·1)	54 (16·0)	117 (34·6)	36 (10·7)	124 (36·7)	25 (7·4)

TABLE VI—SERVICES NEEDED BY PATIENTS WHOSE DISCHARGE WAS DELAYED FOR SOCIAL REASONS

Type of hospital	Number of patients	Services needed					
		Outpatient investigation	Outpatient treatment	Domiciliary nursing	Domiciliary medical care	Domestic services	Other
General and special	82	6	7	24	58	32	17
Chronic	256	..	9	144	71	181	62
All types	338 (100%)	6 (1·8)	16 (4·7)	168 (49·7)	129 (38·2)	213 (63·0)	79 (23·4)

DISCUSSION

The results of this survey suggest that the proportion of patients in general and special hospitals who, on medical grounds, need not have been admitted was 1·6%. (In the present context our data for chronic hospitals are not included.) This figure is based on all Birmingham hospitals, however, and for purposes of comparison with the two surveys referred to below, we restrict attention to three large general hospitals. The proportion of patients considered not to have required admission on medical grounds was 4·0% in all medical wards and 2·9% in adult medical wards.

These estimates are much lower than that of Crombie and Cross (1959) who concluded that a quarter of the patients in the medical wards of a Birmingham hospital in 1955 "had no diagnostic or therapeutic requirements at hospital level". Corresponding estimates obtained by Forsyth and Logan (1960) in adult medical wards of Barrow-in-Furness hospitals were a quarter for males and two-fifths for females.

In appraisal of these results account must be taken of the following differences between the methods of the three inquiries:

1. Crombie and Cross considered patients who died or were discharged from hospital over a period of one year, whereas the other two surveys were based on those in hospital at the time of assessment. The former method gives a somewhat higher proportion of short-term admissions.

2. There are some differences between types of patients admitted to Birmingham and to Barrow-in-Furness hospitals.

These differences in method could account for only a small part of the variation in the results, for which an explanation must be sought mainly in the methods of assessment.

The assessments were inevitably subjective, made in one case (Crombie and Cross 1959) by a general practitioner after consideration of case-notes and patients' home circumstances, in another case (Forsyth and Logan 1960) by the investigators after discussion with consultants, and in our own survey by the consultant or registrar responsible for each patient. We shall restrict our consideration of possible explanations for the differences to the two Birmingham inquiries.

With the assistance of Dr. Crombie we have reviewed the needs of 158 patients (116 adults and 42 children) who at the time of our inquiry were in the medical wards of the hospital which he had surveyed in 1955. According to the original physicians' estimate 6 (3·8%) of them did not, on medical grounds, require admission. Dr. Crombie examined the case-notes and concluded that according to the criteria which he had previously adopted 35 (22·2%) needed "no diagnostic or therapeutic requirements at hospital level". Our main task is to account for the difference of 29 between this figure and the physicians' estimate.

These 29 patients were discussed individually and in detail with the physicians concerned. It emerged from this discussion that in 15 cases judgment had been influenced by the personal circumstances of the patients, and that, if assessed solely in relation to medical needs, they need not have been in hospital. The physicians were satisfied that the other 14 patients could not have been cared for at home, however favourable the home circumstances and domiciliary services.

The revised estimate, based on the physicians' reappraisal of the proportion of the 158 patients who, on medical grounds alone, need not have been in hospital is therefore 13·3%. This figure is about midway between the original estimate and that of Crombie and Cross (1959) for patients in medical wards. The question arises whether it represents the extent to which hospital admission could be reduced by improved domiciliary services and housing conditions.

In the physicians' judgment, of the 21 patients (13·3% of 158) considered not to need hospital care on strictly medical grounds, there were 6 whose admission was attributable directly to housing or other circumstances which might possibly be regarded as remediable. Even in these cases, however, home care would require changes which would be difficult to bring about—e.g., the presence of relatives or friends who were not in fact available. But in the remaining 15 cases the circumstances were so complex that in the view of the physicians it was doubtful whether they were remediable. Admission was determined not merely by lack of specific home facilities or services but also by the state of mind of the patient or relatives and by the relationship between the general practitioner and the patient.

Although these conclusions are based on the small group of 158 patients for whom data were available, we have no reason to think that they are unrepresentative of all patients in the medical wards of the acute hospitals in the city. They suggest that, although about 13% of patients did not require admission on strictly medical grounds, the scope for reduction in the frequency of admissions by improved domiciliary services and housing conditions is much smaller than this figure would suggest.

To permit comparison with the two previous surveys this discussion has been restricted to patients in wards of acute hospitals. The proportion of patients in chronic hospitals considered not to need admission on medical grounds was much higher than in the acute hospitals. It seems probable therefore that it is mainly in chronic and mental hospitals that improvements in domiciliary medical and social services can be expected to make their impact on the pattern of admission.

SUMMARY

During the 1958–59 winter, hospital physicians assessed the medical need for admission of all their patients in Birmingham acute and chronic hospitals. The proportions who could have been cared for at home were 1·6% and 11·8% respectively.

Of patients in the medical wards of three large general hospitals, 4·0% were considered not to have needed to be admitted on medical grounds. This estimate is much lower than that of Crombie and Cross (1959), who concluded that a quarter of the patients discharged from or dying in the medical wards of one of these hospitals "had no diagnostic or therapeutic requirements at hospital level".

The difference between the estimates was examined by reappraisal of 158 patients who were in the medical wards of the same hospital at the time of the survey. 21 (13%) did not need hospital care on strictly medical grounds, but there were only 6 cases (4%) in which admission might conceivably have been prevented by augmented domiciliary medical and social services. In the remaining 15 cases non-medical needs were complex and probably could not have been met by improved services.

These results suggest that it is mainly in chronic and mental hospitals that improvements in domiciliary medical and social care can be expected to make their impact on the pattern of admission.

13·1% of the 4274 patients included in the survey were awaiting discharge; three-fifths of them were delayed for social reasons. The possibility of discharge, as of avoidance of admission, turns upon home circumstances as well as domiciliary services.

The investigation on which this report was based was supported by a grant from the Nuffield Hospitals Trust.

It is with pleasure that we acknowledge our indebtedness to Dr. D. L. Crombie and to the many physicians and surgeons in the Birmingham hospitals who assisted us in the investigation.

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INFLUENCE OF AGE ON TYPE OF HOSPITAL TO WHICH PATIENTS ARE ADMITTED

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IT is well recognised that patients in each of the main classes of hospitals are not homogeneous in respect of their medical needs. This is most evident in chronic hospitals, where some patients require only simple nursing, others mental supervision and training, and still others the full resources of a modern hospital; and in mental hospitals, where patients may exhibit the full range of mental and physical illness. But heterogeneity is by no means unknown in general hospitals, where patients may be retained for social reasons when they no longer need the facilities for investigation and treatment there provided. It has been suggested that a better basis for hospital planning would be a regrouping of patients according to their medical and nursing requirements, ignoring traditional distinctions between physical and mental illness, and between younger and older patients (McKeown 1958).

As a possible basis for such a regrouping, Birmingham patients in chronic (Lowe and McKeown 1949) and mental hospitals (Garratt, Lowe, and McKeown 1958) were assessed individually and placed in four classes determined by their medical and nursing requirements at the time of the survey:

a. Those needing the full resources of a modern hospital—skilled nursing, laboratory investigation, surgery, &c.

TABLE I—LOCATION OF ALL BIRMINGHAM RESIDENTS IN HOSPITAL

Type of hospital	Age (years)						Total
	<15	15–	45–	65–	75–	85–	
General and special	98·4 (601)	52·9 (960)	36·1 (867)	24·7 (322)	12·8 (163)	5·5 (23)	37·5 (2936)
Chronic sick	1·6 (10)	1·2 (21)	6·2 (148)	22·1 (288)	46·2 (589)	67·1 (282)	17·1 (1338)
Mental ..	..	46·0 (834)	57·8 (1388)	53·3 (695)	41·0 (523)	27·4 (115)	45·4 (3555)
Total ..	100% (611)	100% (1815)	100% (2403)	100% (1305)	100% (1275)	100% (420)	100% (7829)

b. Those needing limited hospital facilities—essentially simple nursing care without mental supervision—because of physical illness.

c. Those needing limited hospital facilities—essentially supervision and training—because of mental illness.

d. Those needing no hospital facilities and retained chiefly for social reasons.

When this classification was first made no data were available for general hospitals, whose patients were assumed to require full hospital care. It was clearly desirable to determine whether in general hospitals the proportion of patients not in need of full hospital care is significant, and for this purpose the earlier investigations were extended to all Birmingham general and special (pædiatric, chest, orthopædic, &c.) hospitals. Because circumstances in hospitals for the chronic sick had changed to some extent since the previous inquiry (in 1948) it was also thought desirable to reassess the needs of their patients. The assessment on which the present report is based was made in the winter of 1958–59, and covered all Birmingham patients in hospitals other than mental hospitals. The latter had been surveyed during 1957, and taken together the results of the two investigations provide an up-to-date picture of the whole hospital population drawn from the City of Birmingham.

The method of assessment was the one used previously. The needs of each patient at the time of the survey were evaluated by the consultant or registrar responsible for his care, and details recorded on a form by another doctor familiar with the objects and methods of the investigation. Where necessary additional information was obtained from the nursing staff, but no attempt was made to check or extend knowledge of patients' social circumstances by home visits.

RESULTS

Table I gives the distribution of all Birmingham patients between the various types of hospital. At ages under 15 nearly all were in general hospitals; at ages 15–44 there were about equal numbers in mental and general hospitals; and at ages over 45 the majority were in chronic and mental hospitals.

Table II shows the type of hospital facilities which, from

TABLE II—HOSPITAL FACILITIES NEEDED BY ALL BIRMINGHAM RESIDENTS IN HOSPITAL

Hospital facilities needed		Age (years)						Total
		<15	15–	45–	65–	75–	85–	
Full		93·3 (570)	65·1 (1181)	44·9 (1080)	35·3 (461)	28·7 (366)	23·1 (97)	48·0 (3755)
Limited	Without mental supervision	3·6 (22)	1·4 (26)	6·0 (144)	16·8 (219)	29·3 (374)	46·2 (194)	12·5 (979)
	With mental supervision	0·8 (5)	28·2 (511)	41·2 (989)	38·4 (501)	33·6 (428)	26·0 (109)	32·5 (2543)
None		2·3 (14)	5·3 (97)	7·9 (190)	9·5 (124)	8·4 (107)	4·8 (20)	7·0 (552)
Total		100% (611)	100% (1815)	100% (2403)	100% (1305)	100% (1275)	100% (420)	100% (7829)

the assessment provided by consultants, patients were considered to require. The proportion needing the full facilities of a hospital fell regularly from about 9 in 10 (ages under 15) to 1 in 4 (ages 85 and over) and there were corresponding changes in the proportions needing limited facilities, with or without mental supervision. Approximately 7% of the patients in hospital at the time of the survey did not require hospital care, and this proportion did not vary greatly with age.

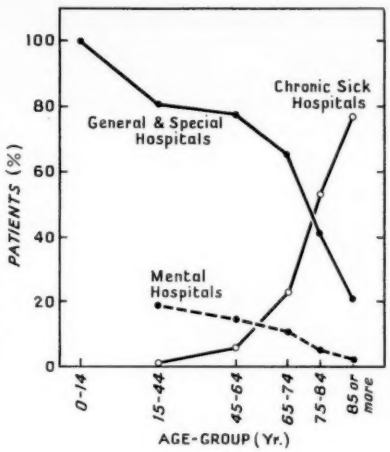

Fig. 1.

In order to determine whether the type of facilities in which patients were placed was appropriate to their needs it was only necessary to combine the data used to prepare tables I and II. We consider first the location of those requiring full hospital facilities (fig. 1). At ages under 15 nearly all were in general and special (including pædiatric) hospitals, but this proportion fell to 4 in 5 at ages 15–44 and to 1 in 5 at ages 85 and over. The most striking feature of the data is the high proportion of elderly patients needing full hospital facilities who were cared for in chronic hospitals (approximately 4 in 5 at ages 85 and over).

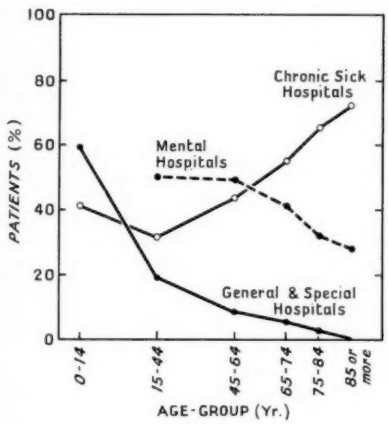

Fig. 2.

Fig. 2 shows the location of patients needing limited facilities without mental supervision. These are the patients usually referred to as chronic sick; most of them were bedfast and needed simple nursing care—washing, dressing, feeding, lifting, attention to bladder and bowel, &c.—but were not under active investigation or treatment. They were distributed quite arbitrarily between mental and chronic-sick hospitals according to age (fig. 2). A considerable proportion of the youngest patients of this type were in general and special hospitals, but their contribution to the total (all ages) is of course small.

The most striking trend in relation to age is, however, in the distribution between mental and chronic hospitals of patients needing limited facilities with some supervision because of their mental state (fig. 3). At ages under 65 almost all of them were in mental hospitals, but above this age the proportion in chronic hospitals rose steeply, and at 85 and over it was higher than in mental hospitals.

We have also examined the location of the 552 patients who were considered not to need hospital care. Approximately 80% were in mental hospitals, 15% in chronic hospitals, and 5% in general and special hospitals. The proportion in mental hospitals fell sharply with age, whereas the proportion in chronic hospitals increased.

Finally, table III gives the distribution of the 7829 Birmingham residents in hospital according to the type of hospital and the nature of the facilities required for their care. Of all patients, approximately half were thought to need the full resources of a modern hospital, a third to need limited hospital facilities with mental supervision, and a tenth to need limited facilities (essentially basic nursing) without mental supervision, while the remainder (7%) needed none of the services which hospitals uniquely provide. The data emphasise the mixed character of patients in chronic and mental hospitals, but show that those in general hospitals are fairly homogeneous (96·8% were thought to need full hospital facilities). These results suggest that the assumption previously made (McKeown 1958)—that almost all patients in general hospitals today require the full facilities of a modern hospital—was not seriously in error.

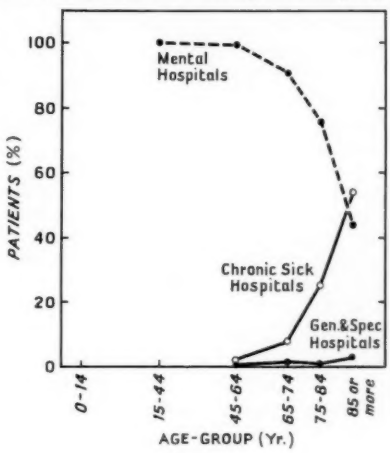

Fig. 3.

DISCUSSION

In a previous communication it was suggested that the traditional divisions between general, mental, and chronic hospitals were attributable to historical circumstances rather than to patients' needs for medical and nursing care (McKeown 1958). Because the mentally ill and the destitute sick presented to society at different times and as different problems, they were segregated from general hospital patients, and their care was assigned to separate

TABLE III—TYPE OF HOSPITAL FACILITIES NEEDED BY ALL BIRMINGHAM PATIENTS IN HOSPITAL

Type of hospital	Hospital facilities needed				Total
	Full	Limited without mental supervision	Limited with mental supervision	None	
General and special	96·8 (2841)	1·6 (48)	0·5 (16)	1·1 (31)	100% (2936)
Chronic sick	34·0 (455)	43·7 (585)	16·3 (218)	6·0 (80)	100% (1338)
Mental ..	12·9 (459)	1·7 (59)	73·0 (2596)	12·4 (441)	100% (3555)
Total ..	48·0 (3755)	8·8 (692)	36·1 (2830)	7·1 (552)	100% (7829)

staffs and administrations. From these divisions there resulted the unfortunate distinction between acute and chronic illness, and the heterogeneity of patients in each of the major classes of hospitals, which is at the root of our difficulties in planning a rational and flexible hospital system.

Since 1948 all hospitals in Great Britain have been brought under common administration and finance, and it might be thought that this would have led to regrouping of patients according to their needs. The results of the present inquiry suggest that there has in fact been remarkably little change. The main difference is that whereas the common feature of patients in chronic hospitals was formerly their destitution, it is now their advanced age.

Indeed, age has become the predominant influence which determines the type of hospital to which a patient is admitted. Irrespective of their needs for care, physically ill patients are almost always in general and special hospitals if they are young and in chronic hospitals if they are old. Moreover, the effect of age on location of patients is not restricted to the physically ill. The distribution of mentally disturbed patients who do not need the full services of a modern hospital (fig. 3) between mental and chronic hospitals is sharply related to age, and at ages 85 and over there are more of such patients in chronic than in mental hospitals.

These results indicate that the heterogeneity of patients within the same hospital has been little affected by replacement of destitution by age as a major influence on the location of patients. They suggest that it will be essential to regroup patients according to their needs for medical and nursing care, rather than their age or the distinction between physical and mental illness. It is only in this way that patients with similar needs can be brought together in facilities designed and staffed in relation to their requirements. We have previously stressed the advantages of locating these varied facilities on a common site (McKeown 1958).

Finally, we should perhaps distinguish between these proposals and the much discussed concept of "progressive patient care". It is no reflection on the merits of progressive care to say that it attempts to improve the arrangements for care of patients in the general hospital without challenging the basis of selection of such patients. The proposals described above, and referred to elsewhere as "a balanced hospital community", are concerned primarily with the distribution of patients between the major classes of hospital—general, mental, and chronic. They could be developed with or without the additional advantages attributed to progressive patient care.

SUMMARY

An assessment of the needs of all Birmingham patients in hospital shows that their distribution between mental, chronic, and general hospitals is determined largely by their age.

Those needing the full facilities of a modern hospital (fig. 1) are in general or mental hospitals if they are young, but in late life they are mainly in chronic hospitals. Those needing limited hospital facilities, with or without mental supervision (figs. 2 and 3) are distributed arbitrarily between chronic, mental, and general hospitals according to age rather than the type of care they require.

These results show the desirability of removing the traditional divisions between the major classes of hospitals and placing patients in facilities which are appropriate to their needs.

The investigation on which this report is based was supported by a grant from the Nuffield Provincial Hospitals Trust.

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Special Articles

HEALTH SERVICE IN SCOTLAND

IN Scotland last year [1] the infant mortality (26·4 per 1000 live births), the maternal mortality (0·3 per 1000 total births), and the number of deaths from respiratory tuberculosis (472), were the lowest ever recorded. There were no deaths from diphtheria, and only 6 notifications of paralytic poliomyelitis. But medicine and public health have had their successes chiefly among the young. The number of deaths from cancer of the lung (2422) has doubled compared with ten years ago: in 1952–56, of 26 countries studied,[2] Scotland had the highest death-rate from this cause (600·5 per million men, 91·2 per million women); and since then the rate for men has risen to 780 per million. The death-rate from bronchitis, too, is one of the highest in Europe, though there is hope that clean-air zones may reduce this disease.

Two new experiments to foster cooperation between the branches of the service are being discussed: a small medical building for Cumbernauld New Town with accommodation both for family doctors and for local-authority maternity and child-welfare clinics; and two consulting suites for family doctors in an extension of the cottage hospital at Huntly, Aberdeenshire.

Hospital boards are drawing up ten-year plans—specific projects in the first five years, more provisional long-term planning for 1966–70. During the year the completed schemes included an extension to Victoria Hospital, Kirkcaldy, reconstruction at Glasgow Royal Maternity Hospital, a limb and appliance centre at Belvidere Hospital, Glasgow, and a new biochemistry laboratory at Edinburgh Royal Infirmary; and 11 major building schemes are in progress.

Work-study teams have now operated for more than a year in the hospital service; the report says that they have assisted both in planning new projects and in raising efficiency in the existing hospitals, often with substantial savings in running costs. A work-study bulletin is issued regularly, which abstracts data from within and without the health service, and from outside Scotland.

A new scheme of hospital morbidity recording is to be introduced for inpatients, to find out the conditions for which patients are treated, how long treatment lasts, and how effective it has been. Eventually the scheme may be extended to outpatients.

The poor state of children's teeth is discussed in a report, *Our Children's Teeth*, by the Scottish Standing Committee on Dental Health Education. Increased dental decay is associated with increased consumption of sweets, lollipops, fruit drinks, and biscuits between meals. A five-month pilot study has been started in Dundee, directed particularly to the age-group 5–12 years, to ascertain the best ways of educating in dental health. A survey was made of the oral hygiene and eating habits of 1200 children starting school; and the results will be compared with those of a similar survey after the study is completed. Encouraging reports of children being persuaded to take care of their teeth come from a school in Sutherland, where the headmaster and staff have discouraged the eating of sweets between meals, and emphasised the importance of brushing the teeth. Treatment is willingly accepted; and in fact only half the children examined require it, and many require very little.

1. Report of the Department of Health for Scotland, 1959. Part I. Health and Welfare Services. H.M. Stationery Office. Pp. 90. 5*s*.
2. *Epidemiological and Vital Statistics Report*, 1959, **12**, 221.

Symposia

RENAL DISEASE

Renal Disease was the subject of a symposium held by the Royal College of Physicians of Edinburgh on March 25.

PATTERNS OF RENAL FAILURE

In a Sidney Watson Smith lecture Dr. J. S. ROBSON pointed out that several diverse water-losing syndromes were explicable on the basis of changes in the counter-current system of Wirz. Hyperparathyroidism, potassium deficiency, hydronephrosis, and pyonephrosis, the action of mercurial diuretics, and the physiological inability of the newborn to concentrate urine were all characterised by reduction in intrarenal water transport resulting from reduction in the normal hyperosmolarity in the medullary pyramids.

In renal failure associated with febrile illness with increased metabolism, uræmic changes could occur despite continued formation of 1–2 litres of urine per day. In acute renal failure (tubular necrosis), renal blood-flow might be greater than the few earlier estimations suggested; and Dr. Robson mentioned a case, studied by the radioactive-krypton method, with a flow of 25–50% of normal during the oliguric phase. He had found septicæmia as the precipitating cause of tubular necrosis in 14 cases of a personal series of 60; *Escherichia coli* and/or *Staphylococcus aureus* were the pathogens. Hæmodialysis could be relied on to correct biochemical changes, but the special liability of the uræmic patient to secondary infection remained the important unsolved problem. He deprecated the use of prophylactic antibiotics in this situation, and strongly favoured deliberate specific therapy on the basis of a full antecedent bacteriological diagnosis, including sensitivity tests.

Dr. Robson made a plea for the general adoption of the Brønsted-Lowry nomenclature, in order to rationalise disorders of hydrogen-ion concentration. The current usage relating "acid" with any anion and "base" with any cation led to confusion, which could be avoided by definition in terms of hydrogen-ion acceptors and donors. All forms of renal acidosis were related to tubular defects of hydrogen-ion excretion or of base bicarbonate reabsorption.

In the correction of severe acidosis by hæmodialysis, he had seen instances in which respiratory alkalosis arose from persisting hyperventilation in the presence of plasma-bicarbonate levels approaching normal. This he attributed to delayed entry of bicarbonate ion into the cells and consequent persisting intracellular acidosis of the respiratory centre. Suggestive proof of this hypothesis was obtained from investigation of the cerebrospinal fluid, in which bicarbonate-ion entry was demonstrably late.

RENAL FAILURE AND ITS MANAGEMENT

In a panel discussion Dr. K. G. LOWE (Dundee) reviewed the development and current role of hæmodialysis and dietary regimens, giving an account of the relative value of conservative management and hæmodialysis. In classifying acute renal failure, Dr. F. M. PARSONS (Leeds) had found renal biopsy valuable for the detection of primary glomerular diseases. In acute reversible renal failure, a rise of the blood-urea-nitrogen by 30 or more mg. per 100 ml. per day indicated a severe uræmic process, which warranted hæmodialysis when the level reached 120–150 mg. per 100 ml. even in the absence of clinical deterioration. The critical level might be as low as 100–110 mg. per 100 ml. with machines of smaller dialysing surface-area than his own. He found that the policy of earlier hæmodialysis reduced the risk of complicating infection. Dr. J. P. MERRILL (Boston, Mass.) had likewise found that the risk of infection was reduced by earlier dialysis; but of some 900 patients with acute renal failure whom he had treated rather less than half had undergone dialysis.

Discussion on the mechanism of unexpected and unexplained death after apparently successful dialysis produced comment on acute multiple infarcts in myocardium and brain and, after repeated dialysis, the possible development of acute microscopic atheroma (Dr. PARSONS). Mr. DAVID BAND, while warning about the need in prostatic obstruction to treat atony of the urinary tract by drainage, agreed with Dr. Parsons and Dr. Merrill that hæmodialysis might expedite preparation for prostatectomy.

Several speakers mentioned the uncertainties surrounding hæmodialysis in chronic renal failure. Some patients might manage without it, while others survived for an unpredictable time with repeated and costly dialysis. Dialysis did not correct the anæmia of renal insufficiency nor did it rectify the abnormal xylose-tolerance curve (Dr. MERRILL).

NEPHROSIS

Dr. MARY MACDONALD described electron microscopic studies of biopsy material from patients with nephrosis. There were characteristic changes in the basement membrane of the glomerular capillaries and the epithelial cells. Typically, the epithelial cells appeared "smeared" and lacked foot processes. Glomerular changes were also found in postural proteinuria.

Dr. G. C. ARNEIL (Glasgow) showed that at least half of a large series of children with nephrosis finally became symptom-free; of the remainder, the majority died; only a few survived over the years with continued proteinuria. He reviewed the changing concepts behind corticosteroid therapy and concluded that, with sodium restriction, an isocaloric diet, and prophylactic antibiotics, steroids had a key role in therapy. To be fully effective steroids might have to be given in long-continued high dosage which produced moon facies and even stunting of growth. Chlorothiazide was used for correction of œdema if steroids failed to stop the proteinuria. Adult nephrosis could be essentially similar to the common childhood variety; but nephrosis recognisably secondary to some other disturbance, such as disseminated lupus, was commoner than in children.

Dr. E. LOVELL BECKER (New York) accepted the Ellis [1] classification of nephritis. In reviewing nephritis produced experimentally by immunologic techniques he emphasised its frequent resemblance to type-1 nephritis. There was some evidence that type-2 nephritis was also associated with an immunologic mechanism. In type-2 nephritis, fluorescein-tagged γ-globulin was taken up avidly by the glomeruli (in the region of the basement membrane), whereas in type-1 nephritis, it was taken up much less by the glomeruli.

RENAL TRANSPLANTATION

In the second Sidney Watson Smith lecture of the day Dr. MERRILL said that rejection of grafts was known to result from acquired hypersensitivity which, not being organ-specific, could be due to exposure to the multiple antigens inherent in nearly all tissues from another individual of the same species. For example, prior skin grafting from a donor might initiate sensitisation in the recipient which would harm a kidney transplanted later from the same donor. Even in transplants between identical twins, where isogenicity ensured absence of reaction to ordinary tissue antigens, he had observed the involvement of the grafted kidney by a glomerulonephritic process. The risk of this seemed to be greatest when glomerulonephritis was the disease which destroyed the recipient's own kidneys. Preliminary excision of the abnormal kidneys might lessen the risk to the kidney which was to be transplanted.

Difficulties with homografts in non-identical twins had directed attention towards suppression of the recipient's reactions to grafted tissue. Early attempts to achieve this by X-irradiation to the point of destruction of the recipient's hæmopoietic system, followed by replacement marrow transfusion, had failed because the marrow did not survive permanently. The new marrow could initiate a detrimental graft-*versus*-host reaction. There were therapeutic possibilities in exposure of the recipient's bone-marrow to sublethal doses of X-irradiation, with or without steroids, or, alternatively, radiomimetic agents such as 6-mercaptopurine. In these circumstances the surviving marrow remnants were "immature" and might resemble the marrow of fœtal life which was known to acquire lifelong nonreactability to any antigens to which it was then exposed. A kidney from an antigenically dissimilar donor could then, in theory, be trans-

1. Ellis, A. *Lancet*, 1942, i, 1.

planted and perhaps survive as well as an autograft. Anti-serotonin agents were also being tried to overcome vascular rejection mechanisms, as were methods of tissue-matching and immune-mechanism saturation by means of massive dosage with donor-tissue antigens. Although kidney tissue was not prone to initiate reactions of the graft-*versus*-host type, and this to some extent favoured transplantation, Dr. Merrill made it clear that kidney grafting other than in identical twins remains an experimental procedure.

In a panel discussion Dr. J. R. ANDERSON (Glasgow) observed, as had Dr. Merrill, that uræmia per se delayed the development of immune reactions to the grafted kidney. Graft-*versus*-host disease appeared to be associated with growth and function of plasma-cells transferred to the recipient with the transplanted tissue. Prof. M. F. A. WOODRUFF emphasised the multiplicity of tissue antigens, the remarkable individuality of their pattern from patient to patient, and the consequent difficulty in attempting to match host and donor.

Prof. R. MCWHIRTER commented on the difficulty of predicting a sublethal dose for bone-marrow as a means of suppressing the immune mechanism. The dose would vary according to the use of supervoltage or conventional equipment. While admitting that such bone-marrow suppression, like radiomimetic agents, carried a risk of subsequent leukæmia, he felt that the risk was acceptable in the circumstances. According to Dr. MERRILL such irradiation was not, in practice, associated with difficulties resulting from post-irradiation excretion of uric acid in excess.

CANCER OF BLADDER

FROM A CORRESPONDENT

A SYMPOSIUM on cancer of the bladder was held in Cairo on March 26–31 under the auspices of the International Union against Cancer, with Dr. HAROLD STEWART (Bethesda, Maryland) as chairman. The choice of Egypt as the meeting-place was apt, for in that country bilharziasis is endemic and the incidence of cancer of the bladder is higher than in European countries or the U.S.A.

The scope of the conference was wide. Information about bladder-cancer rates in Egypt, Africa, Europe, and the U.S.A. was presented. The disease as it occurs in cows in Turkey was described, and the attempts which are being made to elucidate its cause. In discussions on environmental and industrial bladder cancer no new carcinogenic hazards were revealed, but it was abundantly clear that the possibility of a great increase in bladder cancer is ever present in Western countries unless the manufacture and use of chemicals of certain structures are kept constantly under review. It seemed clear that cooperation between industrialists and scientists in this regard is becoming more real, and as our knowledge of the relation between structure and biological action increases (the many gaps in our knowledge were revealed at the conference) preventive measures can be improved.

The main purpose of the conference was to summarise knowledge on the relation of bilharziasis to cancer of the bladder in Egypt. A causal relationship was suggested by Ferguson in 1911,[1] since when a great deal of work has been done to try to establish its nature. There seems to be no doubt that in Egypt the incidence of bladder cancer is relatively high. Bilharziasis is associated with severe forms of cystitis which lead to hyperplasia and metaplasia of the bladder epithelium. Thus an association between bilharziasis and bladder cancer can be accepted, but whether there is a causal relationship is far less certain. Possibly the parasite manufactures a carcinogenic substance in the bladder wall, or it disturbs renal excretion of body metabolites. Other factors such as undernutrition and pellagra may act as co-carcinogenic agents; or perhaps these factors are actually causal. Further investigation is urgently needed in regard to the relation between these two diseases; and the conference made recommendations regarding the lines along which such investigations might be pursued. These would entail very heavy cost.

1. Ferguson, A. R. *J. Path. Bact.* 1911, **16**, 76.

Medicine and the Law

Reasonably Informed

FROM 1932 to April, 1953, a metal grinder was employed in a factory where gas meters were manufactured.

Throughout that time he was engaged on grinding the two-valve seatings in each meter, work which was carried out in three stages. In the first stage the seatings were roughly ground in a mechanised grinder, but in the second and third stages they were more finely ground by means of a slipstone applied manually by the operator. Each slipstone had to be cleaned or dressed before use in the next meter, and for that purpose was rubbed by hand on a circular serrated steel plate upon which silver sand had been sprinkled to act as an abrasive. 144 meters would be so treated every day. In 1948 the deceased became ill and in 1949 idiopathic pulmonary fibrosis was diagnosed. He remained at work but by 1953 he was gravely ill and was admitted to hospital with tuberculosis. In 1955 he died.

His widow sued his employers for damages, alleging that owing to their breach of statutory duty or their negligence they had exposed her husband to the risk of inhaling silica dust from which he contracted silicosis which caused or accelerated his death.

Mr. Justice WIDGERY said that he was satisfied from the medical evidence that the deceased did contract silicosis and that it was a material factor in causing his death.

Any concentration of pathogenic silica dust to which he had been exposed was a low one, but at the date of death the silicosis had become advanced. The medical evidence pointed to a continued exposure to pathogenic dust which continued to aggravate the disease right up to 1953 when he left work and to the tuberculosis having been contracted as a complication of the existing silicosis. At the second and third stages of the grinding processes a relatively small quantity of free silica particles under 5 microns in size were given off and the great majority of them came from the breaking down of the silver sand. The deceased had inhaled pathogenic particles of free silica and, in the absence of any other source, that had occurred while he was working on the grinding operation. The exhaust system installed by the employers was insufficient to protect him from silica dust at all material times up to 1953 and it could with relative ease have been made effective.

But a breach of statutory duty or common-law negligence by the employers had not been established. Section 47 of the Factories Act, 1937, was concerned with processes which gave off a quantity of dust which could fairly be described as " substantial " at the time it was given off, and the dust given off during the grinding processes was not of substantial quantity in that sense. Moreover, though the dust had been injurious to the deceased it had not been shown that such injury was " likely " in the sense that a reasonably informed factory occupier would have foreseen it. Whether the use of sand in a factory process created a silicosis risk depended on whether the process created freshly broken particles below 5 microns in size, but there was no evidence that those technical matters were generally known among employers at the material time. His Lordship was not satisfied that a reasonably informed employer would necessarily have recognised this operation as one likely to create a dust hazard or that these employers had actual knowledge that pathogenic particles of silica were given off in the second and third stages of the grinding process. The widow's claim accordingly failed.

NASH *v.* PARKINSON & COWAN, LTD. *Queen's Bench Division:* Widgery, J. March 24, 1961. Counsel and solicitors: David Croom-Johnson, Q.C., and Alan Lipfriend (Palmer & Robinson); Patrick O'Connor, Q.C., and Ronald Hopkins (Carpenters).

E. M. WELLWOOD
Barrister-at-Law.

In England Now

A Running Commentary by Peripatetic Correspondents

THE East has always been mysterious, and short of the Indian rope trick, which no-one has ever actually seen for himself, fire-walking must surely be one of its biggest mysteries to Western eyes.

Mine must have been wide with wonder as I took off my shoes to enter the sacred territory of the temple forecourt. I had seen the strange procession of yellow-clad figures, bedecked with yellow flowers and with their faces daubed with white, wending their way slowly down the road all day to the sound of weird music and chanting, to a compelling, insistent rhythm of hand-slapped drums. Many had their cheeks and tongues pierced by silver pins like skewers, yet I saw no spot of blood on those notoriously vascular parts. What would I see now, at this climacteric of the day-long ceremony?

I was ushered through a sea of brown faces to a seat at the end of the pit, where a fierce fire of logs was blazing. The heat was tremendous. As it died down the ashes were raked into a white, even bed through which the red embers glowed. And then through the gate at the end of the forecourt came a strange procession. There was no mistaking their appearance now, for they were transformed into an ecstasy beyond this world. The ceremonial marrow was slashed in half, and then the first man went through the fire—slowly, steadily, his gaze fixed in front of him, his feet crunched on the hot ashes. He gave no indication of pain, for he was not then in a world where pain counted. There was a cheer as he reached the trough of water at the end of the pit.

And other men followed, and women, with infants in their arms, and even children, walking steadily through that terrible pit with no sign of fear. A man walked about with a metal pot on his head—a pot in which a fire burned merrily, stoked at intervals with little pieces of stick. Was this what the book of another religion meant when it spoke of heaping coals of fire upon the head? Was this the origin of sackcloth and ashes? And Shadrach, Meschach, and Abednego?

After the last fire-walker had done his penance in the gathering dusk, I went into the inner recesses of the temple for the end of the ceremony. As the procession came slowly through the temple, up the line of little camphor flares that led to the altar-chamber, that strange and persistent chanting reached a crescendo; the hypnotic atmosphere became overpowering, so that I, too, was almost engulfed and overwhelmed. And so it ended, leaving me pondering on the meaning of the whole mysterious occasion.

Next day I took off my shoes as I changed to go into the operating-theatre for the morning list. I almost walked into that sacred territory with bare feet.

* * *

They say that the day of the craftsman is over, but I doubt it. My jeweller tries to give doctors priority for their watch repairs (why I cannot think, for there must be many more deserving occupations than medicine—such as transport operation, the B.B.C., and so on). After two weeks I was making my third call for my watch. Although apparently finished and ready for use, it was still lying on the bench upstairs, so I was told. "I am very sorry, Sir, but the watchmaker puts the jobs in a drawer when they are ready to come downstairs. He is out at the moment, and I dare not touch it. Although this is my firm, these craftsmen have to be treated carefully, and it is more than my life is worth to upset my chief watchmaker."

* * *

The glossy Sunshine Weeklies, which do so much to enable the toiling masses to share rare moments in the lives of the Establishment, today announce that a Mayfair lordling has awarded his steady chick a six-stone engagement ring, thus making a hollow mockery of his piggy-bank.

Until we go metric, six stones = 84 lb. avoirdupois, but even so, reports our Private Eye in the Smart Set, baubles this heavy are a sine-qua-non in such circles. Anything under $^1/_2$ cwt. is regarded as indicative of so much lack of slickness in the chick as to entitle Daddy to demand his money back from her charm school. And, adds Our Man in W.1, very genteel these trinkets appear, clamped neatly on to the appropriate pinky by two $^3/_8$ in. coach-bolts and with a quick-release shackle to allow the attachée a quick dash to the phone in case it's Uncle Harold to say that *of course* Bo-bo must have the Caribbean Embassy job before some ghastly ex-grammar school oik puts in for it.

The bazaar gossip is, however, that one engagement will not now take place because the girl dropped her ring on to her future mother-in-law's foot; and the deb.-of-the-year who was wearing hers when she dived from a yacht at Cannes has been buoyed as a danger to shipping, and the Admiralty is amending its Sailing Directions accordingly.

* * *

He was a pleasant little boy of 8 with a constitutional eczema which had been rather worse recently. I felt there might be some psychological stress upsetting him and after a few simple questions to put him at his ease I asked, "Do you like going to school?" He replied, "I like going to school and I like coming from school, but it's the bit in between I don't like." I now frame my questions more carefully.

* * *

THE SUBLUXATION POLKA

Vy der Vorld iss voll mit drobbles?
Vy your tongue so coated feels?
Vy your skin come out mit bobbles?
Vy you feel like death on wheels?
Vy your bowels not in motion?
Vy, you ask you, vy der heck?
So, I gif you der solution—
Iss from bones, iss in your neck!

All der evils, which we suffer
Dim der youth-light in our eyes
Make us to a crabbed old buffer—
From one simple cause they rise.
Darwin found, iss all from fossils—
Freud find out, iss all from sex:
Otto is der last apostle—
Iss der bones, from people's necks!

Pills and paranoid psychosis,
Damn great pimples coming out,
Cancer, boils and halitosis,
Migraine, impotence und gout—
Vy your mother's aunt iss blotto,
Vy your sister iss ein wreck—
Vy, you ask you, Doctor Otto?
Iss from bones, iss in der neck!

Communism, crime und blisters,
Characters vot chop up frails,
Little boys vot bash their sisters
Or fall in loff mit other males—
Vy der Working class iss striking,
Thinks der bosses stacked der deck?
Iss not wages they are liking,
Iss from bones, iss in der neck!

Vy der vogs don't vorship Eden,
Vy Verwoerdt don't hold mit schpades,
Vy Johannsen's nose iss bleeding,
Vy der Teds got razor blades,
Vy der Government stay in office,
Vy don't Labour see der light,
Vy does folks vant so big profits?
Iss der bones, iss not all right!

Vy iss Marx, und vy iss measles?
Vy iss morals gonned to pot?
Vy we vote for these damn weasels?
Vy mankind iss on der schpot?
Vy dese frightful situations?
Vy iss Russia up to tricks?
All iss due to subluxations—
Noddings iss from politics!

Letters to the Editor

CAN THE NATIONAL HEALTH SERVICE SURVIVE?

SIR,—There is already a shortage of British doctors in both general and hospital practice. In the next few years the gap between total economic demand for doctors and total supply will widen. If it proves impossible to close, the National Health Service will not survive in its present form.

Though the intake of medical students will rise slowly from now, this cannot affect the number of doctors before 1966. To satisfy the probable demand of the late '60s, several new medical schools would have to be opened at once. There is no likelihood of even one opening in the next decade.

The inflow of doctors from overseas will probably continue. In 1949, 600 doctors who were trained overseas registered in Britain, and the number rose to 1300 in 1959. At present most of them take temporary hospital posts and then return to their own lands. But if the shortage of general practitioners intensifies and spreads to consultants, presumably many overseas graduates will obtain permanent appointments in the N.H.S.

Even if clinical assistantships and similar posts are created for general practitioners to help staff the hospitals, this cannot cure the overall shortage of doctors, because most practitioners are already working as hard as they are willing or are able. If they give more time to help the hospitals, they will have even less for their general practices.

It seems likely, therefore, that a growing population will depend on a static or falling number of doctors, from whom it will expect higher standards of care. In such circumstances individual skill, effort, and devotion can have little effect on the total situation, and the quality of medical care in the N.H.S. will decline.

If it does, then private practice will expand. In the early years of the N.H.S. private practice was largely obliterated because medical care of high quality was available to all, free of direct charge. If a service of good quality can be obtained free it is perverse to pay for it. But if the quality declines, the fact that the service is free becomes increasingly unimportant. If the prosperity of the consumer also rises, there will soon be a large demand for private practice, which will gradually attract more and more doctors from the N.H.S. and cause further deterioration in its standards.

In the hospitals, many consultants already give a good deal of time to private practice. It seems possible that, except in teaching hospitals, they will not much longer have the assistance of skilled, highly trained, and mature registrars. In the regions, hospitals may have to depend for their junior staff on newly qualified British doctors or overseas doctors obtaining postgraduate experience. These changes would tend to increase the demand for private specialist care and thus aggravate the difficulty of staffing the N.H.S. hospitals.

If more people turn to private medical care, the pressure to reduce public expenditure on the service may grow. This is likely to lead to higher direct charges to patients and more economy measures. The economy measures will accelerate the decline in quality; the direct charges will remove the advantage of the service being free; and both will further increase the demand for private medical care.

The National Health Service, which has seemed so stable, is thus approaching a critical phase. Unless we take immediate and decisive action, we may well be left with an understaffed service of poor quality, which only those unable to afford private care will use. In this dangerous situation doctors have immense power to help or hinder the reconstruction of the service, because the State will be unable to prevent them withdrawing piecemeal. Indeed the present structure of the N.H.S. ensures that any withdrawal will quickly turn into a rout, because to preserve a balance between the private and public sectors, it contains built-in accelerators. So far, stability has been preserved by a surplus of young doctors, but this surplus is now exhausted.

Radical structural change is therefore urgently needed to safeguard the standards of the N.H.S., and without such change an important experiment will fail.

Richmond, Surrey. J. R. SEALE.

PAVLOV OR FREUD

SIR,—Your leading article (March 4) is a generally fair and balanced statement of the present status of therapy of the neuroses based on learning principles. However, in certain respects the position is better established than you state.

You suggest that the word " learning " is used ambiguously. While there are indeed uncertainties about mechanisms and possible variants of learning, the word itself unambiguously refers to *any* change in habit of response that can be correlated with exposure of the organism to particular stimulus conditions. This, translated into simpler but less exact language, means that learning is a modification of response resulting from experience.

Besides physical growth and organic pathology, learning is the only known process that can lead to alterations in organismal behaviour. That neurotic habits of behaviour are established by learning is a proposition for which there is not only strongly suggestive clinical evidence but also definitive experimental evidence.[1 2] We should expect that neurotic habits would be overcome by applying the learning process in the reverse direction. In the case of experimental neuroses this expectation is consistently fulfilled.[1 2] Experimental neurotic habits can be eliminated at will by means of learning procedures. As you note, increasing data[2 3] points to the effectiveness of such procedures in clinical cases. The connection between what is done by the therapist and what is changed in the patient is usually perfectly clear. Details of technique often have to be tailored to the case, and the effects can very frequently be shown to be stimulus-specific[4]—a central characteristic of phenomena of learning in general.

While endorsing your call for controlled studies to compare the value of conditioning therapy with that of other methods, I do not think that Leigh correctly sums up the position when he states[5] that " learning theory is now in the state in which psychoanalysis was in 1903, when cases were being published of the cure of Frau So-and-so ". To begin with, this implies that psychoanalysis in due course established its effectiveness, which in fact it never did. Since 1903 the psychoanalysts have not produced a single controlled study. On the side of learning theory there is already far more than this or that individual case: hundreds have been reported, in series of various sizes; and a number of controlled studies are being carried out.

Meanwhile statistics give some idea of the way the wind is blowing. Learning theory postulates that the effects of therapies that do not deliberately employ learning principles are due to a non-specific common factor, and that these therapies will

1. Wolpe, J. *Brit. J. Psychol.* 1952, **43**, 243.
2. Wolpe, J. Psychotherapy by Reciprocal Inhibition. London, 1958.
3. Eysenck, H. J. Behaviour Therapy and the Neuroses. Oxford, 1960.
4. Wolpe, J. *J. nerv. ment. Dis.* 1961, **132** (in the press).
5. Leigh, A. D. Section of Psychiatry, Royal Society of Medicine, London, Jan. 12, 1960.

therefore all yield the same proportion of favourable results. In reported series [6] of neurotic patients treated in various ways (including psychoanalysis) a recovery-rate strikingly consistent at about 50% is found. This suggests a broad similarity in the distribution of neurotic patients who attend widely different therapeutic services. Since it is reasonably likely that much the same distribution of cases come to me, the 90% recovery-rate I have reported [2] may be presumed significant.

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JOSEPH WOLPE.

NEUROGENIC HYPERTENSION

SIR,—Your leading article of April 8 rather overstates the evidence for suggesting that cerebral ischæmia may cause chronic hypertension.

In animals the evidence is singularly unconvincing. The work of Rosenfeld [7 8] and Rothman [9] is open to serious technical objections:

(1) Many of the carotid-artery ligations were below the sinus, and the blood-pressure readings of these animals were aggregated with the results of above-sinus ligations.

(2) Even the fact that ligatures were placed above the sinus does not necessarily mean that the sinus nerves were not damaged, since these are very fine and run close to the internal carotid artery. Control rabbits did not have a dummy carotid operation, and I have found that it is easy inadvertently to damage the nerves in such a procedure. In this context the experience of Crandall et al.[10] is instructive. They performed above-sinus constriction in 3 dogs, but on their own criteria there was evidence in these dogs of impaired sinus activity.

I have failed to produce chronic hypertension in 26 rabbits with bilateral above-sinus carotid-artery ligation; great care was taken to preserve the sinus nerves. Even persistent ischæmia of the carotid area is not seen in these rabbits, since the posterior communicating arteries dilate enormously and perfusion pressure is returned nearly to normal levels. Bilateral vertebral-artery ligation in 14 rabbits also failed to produce hypertension.[11]

Whether cerebral ischæmia alone can produce chronic hypertension in any laboratory animal is open to grave doubt; and most workers have probably been studying the combined effects of ischæmia and interference with carotid sinuses.

The data for man are even less convincing. It is true that carotid- or vertebral-artery occlusion sometimes occurs in hypertensive patients. In studies of 17 patients under the age of 40 with carotid-artery occlusion,[12] only 1 was found to be hypertensive; and in studies of blood-pressure before and after acute carotid-artery occlusion (personal observation), a rise has not been observed after occlusion. Even patients with bilateral carotid-artery occlusion may be normotensive,[13] and a survey of retinal-artery pressure readings in a hypertensive population and in carotid-artery occlusion did not yield a single case where obstruction to carotid arteries seemed a likely cause of hypertension.[14] Evidence about vertebral-artery occlusion is more difficult to obtain, but the circle of Willis seems unlikely to allow for long substantially lower pressures in any one part of the circle.

The observations quoted by Roaf,[15] that the giraffe-necked women of Padaung are hypertensive, must await further clarification, but examination of the X-ray suggests that the main site of compression would be at the base of the common carotid arteries, and that a low blood-pressure in the carotid sinus might well be the cause of the hypertension.

The data of Dickinson and Thomson [16] were obtained by perfusion experiments in cadavers, and are open to very serious criticism on technical grounds. These reasons are summarised elsewhere.[17] Briefly, they ignored the effect of resistance in tubing and cannula, which averaged about 66% of the resistance of the artery alone, ranging from 7% to 1250%.

From analyses of these data after approximate correction for cannula size it is clear that:

(1) Cases of renal hypertension do not differ significantly from other types of hypertension.

(2) The most likely reason why the flow in the vertebral arteries is more precisely related to blood-pressure than that in the carotid arteries is that the range of cannula size used in vertebral arteries was half that in carotid arteries.

(3) The data on femoral arteries were obtained at much higher flow-rates and lower internal pressures than in other arteries, and are probably not acceptable as controls.

(4) The results were obtained under conditions of flow and pressure very different from those in life, and their extrapolation to in-vivo conditions is not justifiable.

What Dickinson and Thomson were actually detecting remains uncertain, but it seems likely to be the result, and not the cause, of hypertension. Since the flow was turbulent in most of their experiments, a possible interpretation is that patients with hypertension have atheroma of the carotid and vertebral arteries. Available evidence does not suggest that in vivo this atheromatous roughening causes significant obstruction to flow.[17]

Whether cerebral ischæmia is ever the cause of chronic hypertension in man remains to be demonstrated, but if it is, it is extremely rare.

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ROBERT LOWE.

SHORTAGE OF HOSPITAL STAFF

SIR,—The loss of medical laboratory technicians from the National Health Service to other employment is well known to pathologists, but not sufficiently appreciated by others. A recent advertisement may be mentioned as an example of what is happening.

The current issue of the *Gazette of the Institute of Medical Laboratory Technology* carries an advertisement issued by the United Kingdom Atomic Energy Authority for a "medical laboratory technician". The successful applicant is to be appointed in the grade of assistant experimental officer at a salary of £640 per annum (age 21) rising to £1055 p.a. Furthermore, it is stated that there is a possibility of promotion (with no additional qualification necessary) to the grade of experimental officer, with a maximum salary of £1430 p.a. The minimum qualification demanded for the post is the associateship of the Institute of Medical Laboratory Technology. In the National Health Service the maximum salary payable to a technician so qualified is £720 p.a., almost exactly half the maximum offered by the Atomic Energy Authority. In addition, the advertisement refers to "superannuation, housing, and house-purchase assistance schemes".

In a circular letter distributed to laboratory technicians informing them of recent discussions in the appropriate Whitley Council, the management side is stated to have said: "They knew of no changes in the pattern of responsibilities of the various grades in the two services (presumably the N.H.S. and the Scientific Civil Service) which invalidated the results of their own investigation of comparative duties and responsibilities carried out in 1955." They did, however, undertake to re-examine their attitude in the light of the staff side's conclusions. That such a re-examination may be overdue is suggested by the fact that the duties of the post now advertised, on terms so much more favourable than those in the N.H.S., are described as "mainly routine hæmatology".

Competition for laboratory workers by industry may well be unavoidable; but it is difficult to see why one kind of public service should be enabled to enrich itself in

6. Eysenck, H. J. *J. cons. Psychol.* 1952, **16**, 319.
7. Rosenfeld, S. *Amer. J. Physiol.* 1952, **169**, 733.
8. Rosenfeld, S., Thomas, H. V., Drury, D. R. *ibid.* 1954, **178**, 392.
9. Rothman, S. *ibid.* 1955, **180**, 61.
10. Crandall, D., McCrorey, H. L., Sukowski, E. J., Wakerlin, G. E. *Circulat. Res.* 1957, **5**, 683.
11. Lowe, R. D. To be published.
12. Humphrey, J. G., Newton, T. H. *Brain*, 1960, **83**, 565.
13. Lowe, R. D. *Lancet*, 1961 (in the press).
14. Lowe, R. D. To be published.
15. Roaf, R. *J. Bone Jt Surg.* 1961, **43B**, 114.
16. Dickinson, C. J., Thomson, A. D. *Clin. Sci.* 1960, **19**, 513.
17. Lowe, R. D. *Brit. med. J.* 1961 (in the press).

technical staff in this way at the expense of another. Is there any rational objection to the thesis that people in public service with the same qualifications, doing work of comparable responsibility, in the same or in closely related fields, should be similarly remunerated? One constantly hears of headmasters and youth employment officers advising intelligent boys not to go into the Hospital Laboratory Service. It is clear that, as far as material considerations are concerned, they would be doing less than their duty if they advised otherwise; but this is small comfort for those of us who have to run National Health Service laboratories.

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Reading. F. HAMPSON.

THE CHROMOSOMAL CONSTITUTION OF THE STURGE-WEBER SYNDROME

SIR,—We have recently examined a two-month-old male infant, admitted to hospital on account of convulsions involving predominantly the left side of the body. He had an extensive capillary hæmangioma of the right side of the face, neck, upper chest, shoulder, and upper arm.

Neurological examination revealed exaggerated tendon reflexes. Typical double-contoured calcifications were noted in the skull X-ray. The chromosomes of forty cells in metaphase were counted. Thirty-seven of them had 46, two 45, and one 47 chromosomes. A normal idiogram was obtained from seven metaphases. Capillary hæmangiomas were found in all four of the patient's siblings and in several of his paternal uncles.

Sturge-Weber syndrome is considered to be an example of dominant inheritance with low penetrance. So far no trisomy has been reported in a disease inherited as a dominant except for one instance of trisomy for chromosome no. 22 in a case of Sturge-Weber syndrome.[1] A normal set of 46 chromosomes was found in two other cases of this syndrome.[2] This leads us to believe that trisomy G is not typical of Sturge-Weber syndrome. A normal chromosome complement has also been found in two other phacomatoses—neurofibromatosis,[3] and epiloia.[4 5]

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Iowa City, U.S.A. HANS ZELLWEGER.

Department of Zoology,
State University of Iowa,
Iowa City, U.S.A. KAZUYA MIKAMO.

SIR,—Since Mr. Hayward and Dr. Bower reported a case of Sturge-Weber syndrome trisomic for chromosome no. 22,[6] they and others have reported 16 further cases in which the chromosome constitution is normal.[7–10]

We have examined 2 further cases—a boy and a girl—by skin biopsy and by peripheral blood-culture respectively. In both cases the chromosome number is 46, and analysis of suitable cells shows a normal karyotype.

These cases further support the likelihood that the association in Hayward and Bower's original case was coincidental.

Galton Laboratory,
University College London,
Gower Street, W.C.1. M. d'A. CRAWFURD
J. R. ELLIS.

1. Hayward, M. D., Bower, B. D. *Lancet*, 1960, ii, 844.
2. Lehmann, O., Forssman, H., *Lancet*, 1960, ii, 1450.
3. Harnden, D. G., cited by Sandberg, A. A., Kopf, G. F., Hauschka, G. S. *Amer. J. hum. Genet.* 1960, **12**, 231.
4. Court Brown, W. M., Jacobs, P. A., Doll, R. *Lancet*, 1960, i, 160.
5. Personal observation.
6. Hayward, M. D., Bower, B. D. *Lancet*, 1960, ii, 844.
7. Lehmann, O., Forssman, H. *ibid.* p. 1450.
8. Hayward, M. D., Bower, B. D. *ibid.* March 11, 1961, p. 558.
9. Gustavson, K.-H., Höök, O. *ibid.* p. 559.
10. Hall, B. *ibid.*

THE PHILADELPHIA CHROMOSOME

SIR,—May I say a few more words about your leading article of Feb. 25?

You said that the unusually slow progression in three of the cases reported by Dr. Court Brown and his colleagues supports their view that these cases may represent a distinct brand of leukæmia. I would propose the alternative explanation that in these cases the initial phase of the disease has been unusually long and that the second phase, in which the progressive chromosomal alterations come into being, may yet appear.

I do not believe that the terminal acute phase of chronic myeloid leukæmia is identical with primary acute leukæmia: in the latter disease (and in autonomous new growth generally) the havoc wrought in the nuclei by penetrating radiation, viruses, or chemicals is far more widespread than the circumscript degeneration of a number of genes in chronic myeloid leukæmia. This disintegration of genes is in my opinion not a mutation in the broadest sense of the word, but is due to a more or less quickly increasing lack of inhibitory substances. It is certainly not too much to suppose that similar lesions of other chromosomes may underlie some other tumours. However, as far as I can see, they may be expected only where conditioned tumours turn into autonomous ones—possibly, for example, when prostatic cancer, sensitive to œstrogens and stilbene derivates, loses its sensitivity to these substances.

And now that the existence of the Philadelphia chromosome has become established, we need have little illusion about the curability of the fully developed chronic myeloid leukæmia, in which proliferating disabled cells are distributed throughout the body.

The hypothesis I have put forward [1] may be incomplete, but it has been able to predict the alteration of some genes in chronic myeloid leukæmia, and (if correct) it now shows that the only way out of the difficulties lies in detecting the disease early and in administering the (as yet unknown) physiological inhibitory substances to prevent its development.

Gorinchem,
Netherlands. N. H. D. SCHÖYER.

INDIAN CHILDHOOD CIRRHOSIS

SIR,—I was very interested in the article of March 18 by Professor Singh and others. They make a special point that this condition is typical to the Indian subcontinent, and this is used as an argument for a genetic ætiology. Yet identical cases have been reported from Ceylon, Indonesia, West Africa, Costa Rica, Trinidad, Syria, Lebanon, Egypt, and Israel.

Perhaps the most significant are the findings in Israel, where all cases reported were in children of recent immigrants from Yemen, Iraq, and North Africa, who still use various herbs for treatment and as charms.

The authors also state that no hepatotoxic plants have been found by any worker in India. But in *Indigenous Drugs of India* R. N. Chopra lists a great many plants of the crotalaria, heliotropium, and senecio groups, widely used in indigenous Indian medicine. The common factor is pyrrolizidine alkaloids, which have been shown to be responsible for the veno-occlusive disease in Jamaica and for liver cirrhosis in animals. A commonly used medicinal plant in India is *Senecio vulgaris* Linn, which Chopra mentions as causing liver cirrhosis in animals. Another plant, used for treatment of colic, *S. Jacobea* D. Don, is listed in that book as "poisonous to live stock".

An additional argument which Professor Singh and others give in favour of the genetic ætiology is the fact that the disease not infrequently arises in siblings. But this could just as well be accounted for by custom as by inheritance.

Perhaps the most curious feature of the condition in India is that it occurs in early infancy. This must draw attention to

1. Schöyer, N. H. D. *Lancet*, 1959, ii, 400.

breastmilk as a possible cause, and, indeed, Shoental has shown that rats fed pyrrolyzidine-containing substances excrete them in the milk.

I submit that the possibility of a toxic ætiology is by no means excluded.

W.H.O. Regional Office for South East Asia, New Delhi, India. P. ROBINSON.

HOUSING

SIR,—Since 1956 the best hope of rehousing for people in the London County area whose homes are not due for demolition has been that at least one member of the family should develop a very serious medical condition. Where this is due to, or has been aggravated by, bad housing the doctors concerned have been allowed by the L.C.C. to apply direct on their behalf to the county medical officer of health.

This is very far from saying that such applications are likely to succeed. For the past three years the L.C.C. has had just over 250 dwellings reserved annually for this purpose, excluding tuberculosis cases, and has given out that the number of doctors' applications for them is at least 3000 a year.

Because so many cases have to be turned down, many doctors of my acquaintance have simply given up applying, and one can understand their point of view; but by failing to apply they make this appalling situation look much less grave than it really is.

If it could be shown that there are far more than 2750 unsuccessful applications a year—perhaps five or ten times that number—it might be possible to impress upon the Government that money spent on housing is, time after time, money saved on illness; and, I would add—as a housing consultant—particularly on mental illness.

This, of course, is a national problem. And it is highly relevant that at a time when the cost of the National Health Service is causing the Government so much concern, its estimate for increased expenditure on housing in 1961–62 is a mere £2 million. Doctors may see this as none of their business. Yet a protest from the profession could not fail to carry enormous weight in high places, and it is this backing that the ill-housed and largely inarticulate public most desperately needs.

London, N.W.3. AUDREY HARVEY.

RHESUS-TYPING IN ACQUIRED HÆMOLYTIC ANÆMIA

SIR,—Mr. McLoughlin and Mr. MacKenzie (Feb. 25) make a valuable point. They are of course right that, on occasions, the D antigen of the cells of babies with hæmolytic disease of the newborn may be completely blocked, and not accessible to agglutinating antibody. This is, however, mainly of theoretical importance, because in practice, in the many thousands of cord-blood specimens we have investigated, this phenomenon was seen only very rarely with potent saline agglutinating antisera.

The point which we tried to make in our paper was that patients who have *unsuspected* hæmolytic anæmia may be wrongly typed. It is to our knowledge a universal practice to do Coombs tests on all cord-blood specimens. Hæmolytic anæmia would, therefore, never be overlooked.

Should any doubt remain as to the rhesus type of a baby, in spite of all these precautions, an eluate prepared from the cells would show whether anti-D has coated the cells, a contingency only possible if the latter carried the D antigen. There is, however, no choice in antisera, because, in common with all other acquired hæmolytic anæmias, the cells from these patients are agglutinated by all sera no matter whether the latter contain specific antibodies or not, if they are used as blocking antisera. On the other hand, the position in babies is very much easier than in adults because the overwhelming majority of all babies with hæmolytic disease of the newborn are rhesus-positive (whether the antibody is anti-D, anti-E, or anti-c, &c.). We have encountered only 1 rhesus-negative baby of the genotype Cde/cde whose cells were coated with anti-c; and its cells were agglutinated by AB serum when they were tested in an albumin suspension.

Regional Blood Transfusion Service, Birmingham. W. WEINER.
Selly Oak Hospital, Birmingham. A. M. NUSSEY.

INFECTED COCONUT

SIR,—I read with interest your annotation of March 25, and I should like to record the close cooperation received from the London importers and trade generally dealing in this commodity. Late in 1959 and early in 1960 they were faced, without warning, with a disastrous situation whereby shipment after shipment was being automatically detained at the ports for examination and subsequently the whole or part condemned as unfit for human consumption.

The reaction of the importers was immediate and realistic, and on-the-spot detailed surveys were made available which disclosed appalling conditions of coconut processing in Ceylon.

Intense pressure was maintained upon the Ceylon Government, and draft regulations were prepared applicable to the manufacture and shipping of desiccated coconut which should revolutionise the industry.

A letter dated March 17 from the chairman of the Desiccated Coconut Association in London states:

"I feel sure that you will be interested to know that last evening, four of us had an interview with the Prime Minister and Finance Minister of Ceylon. I can report that they fully appreciated the state of affairs and a cable is being sent, instructing that the New Regulations be set before the Ceylon Parliament, at the earliest possible moment, about 4th April, and they should be implemented by middle or second half of April."

Guildhall, London, E.C.2. J. GREENWOOD WILSON
Medical Officer of Health, Port and City of London.

PYELONEPHRITIS

SIR,—Several points in the interesting paper by Dr. Hutt et al. (Feb. 18) deserve discussion.

(1) At least some of the cases reported as "acute" pyelonephritis might in reality have been "relapsing" pyelonephritis. The patients, in fact, had already been treated with antibiotics and results of some of their renal function tests were abnormal (creatinine-clearance was moderately or greatly reduced in 12 of 14 patients treated). Our observations on 12 cases with typical clinical signs of acute pyelocystitis differed: we found on renal biopsy a marked infiltration of intertubular tissues with leucocytes (indicating inflammatory involvement also of the kidney substance) in 8 of them, but in all 12 cases the creatinine-clearance and the concentrating power were not significantly impaired, while renal blood-flow was only sometimes reduced.

(2) Hutt et al. mentioned the possibility of complete failure or only partial success in treating acute pyelonephritis. Such failures are often due to inadequate and irrational therapy. We maintain that the only hope of preventing acute pyelonephritis progressing to the chronic phase is therapy (alternating cycles of antibiotics and sulphonamides) continued for at least 8–10 months whether or not the urine is apparently sterile.

(3) As for the discrepancies between the renal biopsy and clinical and functional findings in chronic pyelonephritis, among 72 patients with strongly suggestive clinical and functional signs of chronic pyelonephritis who had undergone renal biopsy, we observed apparently normal renal tissue in only 7.[1 2]

1. Campanacci, D., Bonomini, V. *Minerva Med., Roma*, 1960, **51**, 1173.
2. Bonomini, V. *Urol. int., Basel*, 1959, **8**, 177.

Furthermore, when renal biopsy findings were consistent with pyelonephritis, renal function was always impaired. On the other hand, the necessity for performing renal biopsy in the absence of clear clinical or functional signs of renal involvement is doubtful.

(4) We completely agree [1 3] on the need to take all the investigations (clinical, functional, bacteriological, radiological, and biopsy) into account in order to diagnose chronic pyelonephritis correctly. Among the functional tests, we would like to emphasise the diagnostic value of a study of the urinary excretion of H^+ ions (under basal conditions and after oral administration of ammonium chloride). This was first suggested by Brod.[4] We have observed that when azotæmia was normal, urinary excretion of H^+ ions (mostly as ammonium salts) was significantly lower in pyelonephritis (92 cases) than in glomerular nephritis or in vascular nephrosclerosis (133 and 174 cases, respectively).

(5) As for the significance of the white-cell excretion-rate after giving pyrogen intravenously, it is probably true that this test should be recommended for assessing the effectiveness of treatment rather than as a diagnostic procedure.

Institute of Medical Pathology,
University of Bologna, Italy. V. BONOMINI.

EXTERNAL CARDIAC MASSAGE

SIR,—Dr. Jacob's letter (April 1) prompts me to ask a question which I have not seen satisfactorily answered anywhere. Have patients revived by cardiac massage been followed up to find out how long they remained alive?

Reigate,
Surrey. T. W. PRESTON.

REPRINTS

SIR,—The correspondence on reprints is very interesting. Although the demand for reprints can become irritating, as some correspondents stated, those who are inclined to throw any printed card rather contemptuously in the wastebasket risk extinguishing a sincere interest in their own work.

Many people have abandoned the riches of libraries and the other luxuries of a big scientific centre and have settled in an area less developed scientifically and otherwise. Their ambition is to live up to the standards they were trained to, and to raise the level of their country accordingly. Such colleagues would certainly appreciate a reprint more than many people realise. Usually they are not in a position to see the specialised journals and they are happy enough to find the address of the author, so that they can ask for a reprint. Fortunately there are journals that give the contents of other journals, with the addresses of the authors. I have received in that way many special articles of great interest and importance to me.

Those who lack medical libraries and secretaries seldom have funds to pay for reprint requests or to send the requested reprints of their own papers; and they have little time to write letters, because they are striving to make a living under adverse conditions. Whatever they do for science, investigation, and writing, they do " toiling upward in the night ".

An aristocratic society of scientists, lacking sympathy for those who do not confrom to their ideal of writing letters, is to me out of date.

Department of Clinical Therapeutics,
Athens University Medical School,
Alexandra Hospital,
Athens. GEORGE K. DAIKOS.

SIR,—I heard the first cuckoo at 7.10 A.M. today, and two hours later the postman brought 42 requests for reprints. Is this a record for one morning?

East Cheam. EARLY BIRD.

3. Bonomini, V., Zucchelli, P., Biancani, G., Dalmastri, G. *G. Clin. med.* 1959, **40**, 694.
4. Brod, J. *Lancet*, 1956, i, 973.

PSYCHIATRY FIFTEEN YEARS AHEAD

SIR,—The Minister of Health, Mr. Enoch Powell, in his speech to the National Association for Mental Health,[1] said that by the mid 1970s we may need only half as many hospital beds for mental illness. In the future, treatment should be for the most part in wards and wings of general hospitals, though he would " neither forget nor underestimate the continuing requirements of security for a small minority of patients ". This, he said, implied " the elimination of by far the greater part of this country's mental hospitals as they stand today . . . The institutions themselves are doomed ".

From this policy some extremely important questions arise.

1. We can hardly expect that the ideal of *comprehensive* psychiatric hospitals within the curtilage of general hospitals could be achieved. The cost would preclude this. Presumably, therefore, there will instead be relatively small short-stay psychiatric units attached to general hospitals. If so, how will they be administered? Will they accept every type of psychiatric case, like the observation ward of the past, or will they " cream off " those considered most desirable?

2. What will be the lot of the rejects from these general-hospital units—long-stay patients requiring many months or even years of hospital beds, and the incurable and those with gross behaviour disorders? Will the docile go to local-authority hostels and the others to some new security unit?

3. The new policy seems to spring from the wish to integrate psychiatry and general medicine. But should the psychiatric hospital itself therefore be brought into line with general hospitals? This has indeed now become legally possible, though it is doubtful whether the Royal Commission on the Law relating to Mental Illness and Mental Deficiency had it in mind. The W.H.O. Expert Committee on Mental Health had some very definite views on this question in their third report (September 1953). To quote: " The more the psychiatric hospital imitates the general hospital, as it at present exists, the less successful it will be in creating the atmosphere it needs " for promoting a therapeutic community. Again: " The psychiatric hospital does not do its job best by imitating the general hospital. Too often the psychiatric wards of a general hospital are forced by the expectations of the hospital authorities to conform to a pattern which is harmful to their purpose."

4. There is a further danger. I quote again from the W.H.O. report: " Psychiatric wards of general hospitals sometimes have another characteristic which may prove very detrimental to the community mental hospital if they are the only portal of entry for patients into the latter. In such a case the general hospital may treat and return to society a high proportion of psychiatric patients capable of early recovery and send to the community mental hospital only those patients who are grossly disturbed, chronic, or of apparently bad prognosis. There is no more certain way of turning the community mental hospital into a ' madhouse ' and depriving it of its role of a therapeutic community." (As there may apparently be no community mental hospitals in the future this situation would apply instead to hostels and security units.)

In the wave of enthusiasm and optimism which has sprung from the Mental Health Act of 1959 and from statistics which show a decrease in the number of psychiatric inpatients, we must never lose sight of the basic truth that the *nature* of mental illness is essentially different from the ordinary run of medical and surgical illness. From this it follows that the *needs* of psychiatric patients are different too. Their needs are primarily emotional and only secondarily physical. Most psychiatric patients, being physically well, are " up and about " all day and must have adequate space and facilities for a wide variety of activities with a view to full resocialisation. Treatment must therefore be given where there is an organised community life. As a corollary to these needs there must be specialised training for the development of a therapeutic attitude on the part of all the different types of staff.

1. *Brit. med. J.* March 18, 1961, p. 820. *Lancet*, March 18, 1961, p. 608.

Eventually we shall have to make up our minds whether there is anything of value in our present community mental hospital service worth preserving. Many experienced people believe that general hospitals have something to learn from the therapeutic atmosphere, organisation, and administration of our psychiatric hospitals, and that it would be unfortunate for medicine as a whole if the culture of the psychiatric hospital was to be swallowed up in a grand " take-over bid ".

In my view we need to strive for much closer integration between general medicine and psychiatry (and better liaison with general practitioners and local authorities), and for this to be obtained there are three main requirements: (1) much better psychiatric education of the medical student; (2) many more comprehensive nurse-training schemes; and (3) small psychiatric wards in general hospitals for cases selected primarily for teaching purposes. It would not be in the best interests of psychiatric patients as a whole for every case requiring inpatient treatment to be treated first in a general hospital. This would lead to a recrudescence of stigma and decreasing standards of treatment for long-stay and incurable patients. Their chances of recovery would be lessened and their isolation increased. Dr. Baker emphasised this in his article in your issue of March 25 when he said:

" Treatment in the mental hospital depends on the attitudes, the expectations, and the morale of those who work in it. Successful rehabilitation needs an atmosphere of therapeutic optimism. We have shown that an active therapeutic regime produces worthwhile results among admissions and long-stay patients alike, and steadily reduces the total number of patients in the hospital. A change in attitude or a fall in morale, however produced, could readily refill these same empty beds."

Perhaps the most questionable feature of some of the contemporary thought on psychiatric problems is the expectation that in fifteen years' time the long-stay and incurable patient will have virtually disappeared and so mental hospitals could then be pulled down. Because many of these institutions are vast, " majestic and imperious ", and geographically isolated from the communities they serve, it does not follow that in principle a specialised hospital, providing a comprehensive psychiatric community service, is wrong. If we cannot have such a hospital within the general hospital curtilage, let us continue to develop suitable existing hospitals along progressive lines where the local situation is favourable.

Moorhaven Hospital,
Ivybridge. FRANCIS PILKINGTON.

TRAINING FOR CHILDBIRTH

SIR,—So Dick Read was " unscientific ", it was suggested at the meeting you reported last week (p. 765.) Having seen at least four striking cases of spontaneous painless labour, he spent years intently observing the emotions and difficulties of pregnant and parturient women, and confirmed his idea that physiological labour shorn of cultural errors is actually a quite bearable experience and ideally ought to be painless (was meant to be, is naturally, painless). Had he seen four samples of pure iron, and then said pyrites " ought " to provide pure iron under proper conditions, would he be unscientific?

To suppose that painless labour is induced solely by the impress of " personal influence " and a confiding sense of security is rather like saying that education has an emotional setting but no truth content; that an engagement ring needs either no gem or that glass will do. Certainly the arts of the teacher have to be applied; failure and success mark the difference between intellectual comprehension of a truism and the emotional seizing of it in governed action.

Some Russian, I imagine, having read one of the eight extant foreign translations of Dick Read's books, said " Party angle that, Prof.!" The professor saw that the well-trained patient entered labour having in her head a firmly integrated set of ideas of behaviour and in a rapturous state of Pavlovian inhibition he cried " Eureka! " Pavlov took the credit some years too late, but Russian pressure and prestige and Russo-Franco-Sino energy and enterprise soon bore fruit in mass statistics of success that no English obstetricians can rival. But of course Dick Read was " unscientific "!

London, S.W.1. W. THOMSON BROWN.

THE METRIC SYSTEM

SIR,—Our factory has recently changed over completely to the metric system, but not without one or two teething troubles. As previous correspondents have pointed out, the real difficulty and danger is the insignificance of the " point ", and we find this especially in reading the second or third carbon copy of our manufacturing records. Another difficulty is that for many of our process workers this is their very first contact with the metric system in practice.

In order to prevent mistakes, we draw attention to the decimal point by associating it with the abbreviation letter. In our system, 1·5 litres becomes 1L·5 and 2·65 kilograms would be written 2K·65. There would seem to be no reason why this system should not be extended to cover grammes, milligrammes, and millilitres.

Chandler's Ford,
Hampshire. J. GREGORY.

GENERAL PRACTICE

SIR,—Dr. Evans and his colleagues (March 18) are to be commended for stimulating interest in the future of general practice. They must be numbered among the doctors—unfortunately a minority—who were very disappointed with the report of the Pilkington Committee. Considering the time taken and the nature of the evidence submitted and asked for, some really radical and important recommendations were confidently expected instead of the relatively simple pay award which trade-union representatives could have obtained in a few weeks.

They raise several important points; but there is at least one serious omission—the role of the general practitioner in the field of preventive medicine and all that this implies in close cooperation with the local health authority and other social workers.

These agencies have for the most part the same functions as ourselves—namely, to provide family medical services to our patients within the background of home and place of work. They are especially interested in the preventive aspects of clinical and social medicine, and this should also concern us. It is manifestly absurd and needlessly expensive that at this time these two branches of our medical service should be run separately and on parallel lines. Further, it is becoming increasingly evident that the day of the single-handed general practitioner is passing. All over the country doctors are joining together in groups, which vary from simple duty rotas to full partnerships. In the interests of economy and efficiency it is clearly best for a group to practise from a common surgery; surely the next step is for the group to be closely associated in the same building with health visitors, district nurses, and other social workers. In my opinion these premises should be built and maintained in the same way as the hospitals, out of central funds.

In general practice under these conditions many of the desiderata mentioned by Dr. Evans and his colleagues would be attained without much difficulty. The ancillary services provided would relieve the general practitioner of much routine work, leaving him more time to devote to his patients, and

facilitate full participation in the preventive medical services—e.g., infant welfare, inoculations, school inspections, and so on. Provision of some diagnostic equipment and a treatment-room would allow scope for the exercise of special interests and skills. There would be no difficulty in finding cover for holidays, postgraduate study, or when hospital posts were taken as suggested by the Platt committee. Working in close contact with colleagues does have a stimulating effect, and this is the best way of raising our standards of service.

If we are to have a renaissance in general practice we must first put our house in order; but we cannot do everything ourselves. Although we may not qualify for the same scale of remuneration as consultants, we ought to have the same scale of facilities for doing our work.

William Budd Health Centre, Bristol. JOSEPH SLUGLETT.

POSTCARDIOTOMY SYNDROME

SIR,—In reading Dr. Smith's paper last week we were particularly interested in its bearing on the cause of the postcardiotomy syndrome. During the first few years of our experience with mitral valvotomy the syndrome occurred in approximately 5% of cases. There was nothing to suggest that it was due to a recurrence of rheumatism. It was our custom to repair the pericardium after valvotomy and a relationship between the syndrome and retention of blood in the pericardial sac was therefore suspected. This relation now appears probable since in more than 400 consecutive cases of mitral valvotomy in which the pericardial recesses have been carefully cleared of blood, the syndrome has not been seen. It is perhaps supporting evidence that of 100 cases of reoperation for mitral stenosis, in which, of course, the pericardial space is nearly always totally obliterated, none has been complicated by the postcardiotomy syndrome.

ANDREW LOGAN
RICHARD TURNER.
Edinburgh.

THE USE OF TELEVISION IN X-RAY DIAGNOSIS

SIR,—The comprehensive description by Dr. Stevenson and Mr. Fergusson (April 1) of 'Vidicon' industrial television cameras in conjunction with 5, 7, and 9 in. image intensifiers will, without doubt, encourage a much wider application of these techniques. But to do justice to the rather more general title of this paper, some other developments should be mentioned.

An X-ray image amplifier using $4^1/_2$ in. image 'Orthicon' [1] has been developed in this country within the past two years. Mirror optics with an approximate effective aperture of $f/0{\cdot}7$ project the image from a 12-in. fluorescent screen on to the image orthicon, from which the final image is displayed on television monitors using a triple interlace which gives essentially 16 complete images per sec. and approximately 1000 lines.

A 12-in. TVX television tube [2] is being developed in the United States of America, where photons of X-rays are made to generate proportional electrical energy in the semiconductor tube. This energy is then amplified to form the diagnostic patterns on television-receiver screens.

A recent Dutch development [3] makes it possible to store radiographic images from a television system on a disc coated with a magnetic material, so that the radiographic pictures can be displayed when wanted and for as long as necessary. The disc, like a magnetic tape, can be used repeatedly for the storage of different images.

Janker [4] in his institute in Bonn has designed a remote-control desk which incorporates a number of switches. He is thus able to control 2 television cameras used simultaneously, the X-ray apparatus, a film and still camera (Polaroid Land), focus, contrast, negative or positive reproduction, rotation of the table, and selection of transmission from one or the other camera to his lecture theatre.

Department of Medical Illustration, Guy's Hospital, London, S.E.1. C. E. ENGEL.

1. Garthwaite, E., Haley, D. G. *J. Brit. Instn Radio Engrs*, 1959, **19**, 615.
2. Jacobs, T. E., Berger, H. *Elect. Eng.* 1956, **75**, 158.
3. Oosterkamp, W. J., Schut, Th. G. *Elektr. Rdsch.* 1960, **14**, 19.
4. Janker, R. *Med. biol. Ill.* 1960, **10**, 179.

THE £24,000 QUESTION

SIR,—This may have special importance for doctors, if it means that the Government intends to make the nationalised industries and the Services as efficient as I.C.I. Once this practice is started there is no knowing where it will stop; and, sooner or later, someone will notice that the National Health Service, as a supplier of goods and services, has certain resemblances to both British Railways and I.C.I.: yet it has no general management. It might be argued that a manager at £24,000 a year would find here a fruitful field for his activities.

Liverpool. HENRY H. MACWILLIAM.

ANTINUCLEAR FACTOR

SIR,—Dr. Doniach and her colleagues (March 25) have drawn attention to qualitative differences between antinuclear factor consistently present in the serum of patients suffering from systemic lupus erythematosus (S.L.E.) and antinuclear factor commonly encountered in rheumatoid sera and, less frequently, in other sera.

We agree that these differences exist and that tests for antinuclear factors should be made at a standard temperature. Your correspondents suggest that all antinuclear factors may be considered to be autoantibodies differing one from another (or one group from another) in the range of temperature within which combination with nuclear material occurs. There is good experimental evidence to support the contention that antinuclear factors in S.L.E. are antibodies. We doubt, however, if there is sufficient proof to warrant the inclusion of antinuclear factors present in other diseases in this category. In our own and in others' experience it is unusual to demonstrate precipitating or complement-fixing antibodies directed against nuclear material in the sera of patients with rheumatoid arthritis, even when antinuclear factor is present in high titre as measured by the Coons fluorescent-antibody technique.

In the course of our investigations of the nature of antinuclear factor, we have measured the lytic activity of human sera by their ability to reduce the turbidity of suspensions of organisms susceptible to the action of lysozyme. In most cases of S.L.E. the lytic activity has been within the normal range, even in the presence of a high titre of antinuclear factor. However, in rheumatoid arthritis, the majority of sera containing antinuclear factor in high titre have also shown an increased lytic activity when compared with sera in which no antinuclear factor could be detected.

The possibility that the antinuclear factor in rheumatoid arthritis may be an enzyme is indicated also by our demonstration, using the Coons technique, that a number of plant and animal enzymes have specific affinity for the nuclei of cells in unfixed tissues and blood films. The distribution of fluorescence in these preparations is indistinguishable from that observed with positive sera in the test for antinuclear factor. Enzymes possessing "antinuclear" activity have, without exception, been shown also to have lysozyme activity, and human tears, well known to be rich in lysozyme, impart nuclear fluorescence when labelled with rhodamine B.200.

We feel that these results support the thesis that antinuclear factor in rheumatoid arthritis differs from

antinuclear factor in S.L.E., not only in its thermal range of activity but in the class of proteins to which it belongs.

These investigations are at an early stage, and it would be rash to lay too much emphasis on the possible significance of our results. We present them, however, as an alternative explanation for your correspondents' observations on the heterogeneity of antinuclear factors and to emphasise that antibodies are not the only proteins which react with nuclear material.

Rheumatic Diseases Unit, Northern General Hospital, Edinburgh. W. R. M. ALEXANDER J. L. POTTER.

WHO IS DELIVERED?

SIR,—Mr. Russell (April 1) is undoubtedly correct in his belief that it is the mother who is delivered. To the quotations which he gives from the Bible two further ones could be added.

In *Exodus* we read of the midwives Shiphrah and Puah excusing themselves for not having killed the male sons of the Hebrews by saying "because the Hebrew women are not as the Egyptian women and are delivered ere the midwives come in unto them", and in *St. John* XVI, "a woman when she is in travail hath sorrow, because her hour is come, but as soon as she is delivered of the child, she remembereth no more the anguish". The new English Bible renders this, "but when the child is born . . ." This is also correct and it is high time we started to speak of babies being born. This is not pedantry; by referring to a woman delivering a baby, as one might refer to the butcher boy delivering the meat, we detract immeasurably from the dignity and the danger of childbearing. At the present moment the treatment of women in labour is very much under inspection and it is very important that all in the labour ward or bedroom should realise that the woman is not producing a new plaything for them, she is in fact in travail (and just because it is *natural* it is no less painful, unpredictable, and dangerous) and she needs to be delivered from her travail by every means at the disposal of those in whom she has put her faith.

London, W.1. C. K. VARTAN.

SIR,—Mr. Russell may be interested to know that the Central Midwives Board have recently sought the approval of the Minister of Health to change the wording of the Statutory Instrument concerning the training of midwives, so that the term "delivered" is used intransitively, following the biblical precedent he quoted.

London, S.W.7. ARNOLD WALKER Chairman, Central Midwives Board.

ACCIDENT SERVICE

SIR,—Severe road accidents seem to be an important factor behind the drive for a nation-wide accident service. Many of these accidents are preventable. The medical profession might well regard new buildings, more undergraduate teaching, more nurses, and so on, to deal with road casualties, as it would look upon the opening of hospitals for typhoid fever, diphtheria, and tuberculosis.

The arguments for child labour in the factories were stronger at the time than those which now allow this road disgrace to continue. A way to keep ahead of other countries is to prevent these accidents, not to take up a competition in better buildings. A society which can change the design of oil heaters overnight and remove prostitutes from the streets of London, after an acceptance of hundreds of years, is quite capable of creating conditions to save the lives of its members.

Pondering on the reasons for the rigorous control of air traffic might be constructive. While the new buildings are being planned there are several things which could be assessed—i.e., the use of number plates with figures of a size which can be comprehended when the observer and the observed are moving longitudinally and vertically in cars, control of the alcohol and of speed factors, and streamlining the techniques of applying the law and readjustment of penalties.

Prevention of these accidents should be regarded as practicable. To lie down and mentally accept a permanent high accident and death rate, as at present, and then to attempt to cure the end-result is impracticable and even ridiculous.

London, S.W.19. G. KENT HARRISON.

NOT FOR SALE

SIR,—I had read this leading article (Jan. 14) at the time of publication; and, after reading Dr. Dunlevy's letter (April 1), I have now studied your editorial again without any sense of offence. Far from this being, as Dr. Dunlevy imputes, "an attack on the integrity of a considerable section of the profession" it strikes me as a reasonable effort to point out some of the problems of present-day specialist practice.

In view of your correspondent's allegations, and the fact that such remarks are liable to be freely abstracted in the lay Press, it would seem important to state that these alleged conditions must surely be uncommon. Working as I do in London and the Home Counties I can categorically state that there is no "queue-jumping" for beds in my own hospitals. Furthermore, I rarely see a patient in private who is subsequently admitted to a general ward. The few exceptions are mainly elderly folk who appreciate the greater time and more personal character of a private consultation. No family doctor of integrity would refer, and no consultant of integrity will accept, a regular stream of "guineapigs" for admission as general patients. Indeed I would say that there is a large proportion of general practitioners who (perhaps understandably in view of their own miserable capitation fee) will discourage a patient from seeking private consultant advice even when this is requested.

I cannot agree with Dr. Dunlevy that there is anything wrong in a patient having X-rays or pathological investigations at the hospital after a private consultation. It would, however, be quite unethical if a physician or surgeon deliberately built up a private consulting practice on this basis. But anyone who aspired to build up a good private practice would be most ill-advised to follow such a course. The politicians promised the public that they might avail themselves of the whole service or any part of it; it is not for us, as doctors, to promote or frustrate our patients' exercise of choice in this connection. I advise in my clinic and treat in my hospital beds many patients of private doctors, but I see nothing improper in this. Dr. Dunlevy is under no obligation to give priority to cases other than on strictly medical grounds.

A second point in Dr. Dunlevy's tirade concerns some patients' belief that the consultant personally will operate on them. Surely this is a widespread belief amongst hospital patients and has nothing whatever to do with whether or not they were seen privately in consultation. The operation consent form makes it quite plain that an undertaking has not been given that the operation will be performed by a particular surgeon, and patients normally sign such a form at the time of admission. Despite this I have found that many patients have no idea that they have been admitted to the care of a surgical team, and that any member of that team may deal with the whole or part of their operative treatment. Were this point made clear by the hospital authorities it is likely that a proportion of patients would elect for private rather than "free-at-the-time" service.

Turning to Dr. Dunlevy's stricture on the domiciliary service, I can only say that I utterly disagree with him. The domiciliary service is potentially, if not actually, one of the most valuable features of the N.H.S., though I am not personally convinced of the need or wisdom of making such visits freely available to all and sundry. Fortunately the part-time consultant frequently saves the Treasury the cost of an N.H.S. domiciliary visit when the patient elects to have a private visit. It is nonsense to say, as Dr. Dunlevy does, that "the con-

sultant is guaranteed an extra £800 per year". As a maximum part-time surgeon I do no more than 20 domiciliary visits a year. The records for the North West Metropolitan Hospital Region for 1956 show that 15,531 visits were done by a total of 714 consultants of all grades. The average annually was about 50 visits per physician and 30 per surgeon. So much for Dr. Dunlevy's "guaranteed extra £800 per year"! Whilst I was a member of the medical committee of that same board there were occasional allegations of abuse of the domiciliary service. A number of us repeatedly asked for evidence of these abuses, but none were made known and the senior administrative medical officer admitted that there were no more than occasional dubious cases.

If Dr. Dunlevy has found that some of his colleagues err in their ways I would suggest that he has two methods of dealing with the problem: a direct and frank approach to the doctors concerned, and, failing any satisfactory response, an approach to the ethical committee of the B.M.A. or to his local consultants and specialists committee. I do not know what "non-professional forces" Dr. Dunlevy has linked up with, but I suggest that he would be wiser to stick to existing professional bodies in securing maintenance of those high ethical standards to which any honest doctor must subscribe, and to which the majority of the profession still strictly adheres.

London, W.1. REGINALD S. MURLEY.

SIR,—The morning after Dr. Dunlevy's television interview (April 4) I asked for an inquiry to be carried out into the source of admission of all patients on my medical unit, with the following results:

Patients admitted direct by request of family doctor	33
Patients admitted from general outpatient clinic	12
Patients admitted from casualty department	4
Patients admitted after domiciliary visit	5
Patients previously seen in private consultation	0
	54

Some years ago a personal analysis of 100 consecutive domiciliary visits showed that between a quarter and a third resulted in hospital admission: the remainder being made for diagnostic or humanitarian reasons or, sometimes, to save a hospital bed.

In the light of these figures I wonder if Dr. Dunlevy could produce facts to substantiate the statements made in his letter (April 1) and at his television interview.

Luton and Dunstable Hospital,
Luton, Bedfordshire. T. PARKINSON.

OBSTETRIC ANÆSTHESIA

SIR,—In recent years obstetric anæsthesia has gained the reputation of being a hazardous art.

The main troubles arise from vomiting due to a partially full stomach, for in most instances it is impossible to forecast the need for an anæsthetic; and in any case during labour gastric emptying is grossly delayed.

A number of tragic deaths have stimulated obstetricians to develop the technique of pudendal block. This provides excellent anæsthesia for low forceps delivery; but if the head needs rotation or for other more complicated manœuvres, a general anæsthetic is usually preferable.

To empty a stomach is time-consuming—particularly when every minute counts—and in my experience rarely completely successful, so that in many cases the patient is quite liable to vomit, even though a stomach tube has been passed. So, except in patients known to have consumed much food or drink shortly before anæsthesia is required, I feel it is unjustifiable to subject a distressed woman to a procedure which will probably not make her delivery any safer.

Facilities to deal with the hazard of vomiting from a partially full stomach must be to hand—in particular efficient suction-apparatus, and a bed which can be tilted. It is when such facilities are not available that tragedies occur; and it therefore follows that a general anæsthetic is unsuitable in domiciliary practice, except in grave emergency.

A stormy induction precipitates vomiting and must be avoided. Every anæsthetist must be experienced in dealing with vomiting patients, and able rapidly to intubate the trachea; but—perhaps most important of all—he must have immediately to hand all the apparatus he may require, and this apparatus must always be in full working order.

Afterwards the patient should be put on her side, and not left unattended, for disasters are just as likely to occur at this stage as during induction. The anæsthetist should not leave the building until the patient is fully conscious.

If these principles are adhered to, obstetric anæsthesia is not really such a hazardous art.

Scarsdale Hospital,
Chesterfield,
Derbyshire. DENIS R. COUCHMAN.

NOT EDISON

SIR,—In your annotation (Feb. 18) on medical research, you mistakenly attributed to Edison the comment: "What is the value of a newborn baby?" This is such an apt retort to the practical man that just about every investigator has had the distinction of not having said it.

The honour goes to another American, Benjamin Franklin, on the occasion of a manned balloon flight from the Tuileries (Sept. 19, 1783). A sceptical practical man among the spectators argued the utility of the experiment, asking what good could a balloon be. Ben Franklin thereupon asked: "What good is a newborn baby?" ("Eh! à quoi bon l'enfant qui vient de naître?") The bon mot was quoted all over Paris and then throughout Europe. Franklin gives an account of the occasion in his autobiography.

The quotation has also been erroneously thrust upon Faraday. It seems Faraday had discovered the principle of the dynamo and had a primitive model spinning idly but not toiling fruitfully in his laboratory. Word of the wonderful machine reached Gladstone, who journeyed to see it. After observing it thoughtfully for a while, the future prime minister said: "Very interesting! But what good is it?" To which Faraday replied: "Well—some day you may be able to tax it."

Somerville,
New Jersey. NICHOLAS G. DEMY.

INFANTILE HYPERCALCÆMIA

SIR,—The syndrome of infantile hypercalcæmia seems to be less often seen now, and tends to be milder than in the past.

In 1959 and 1960 I saw 7 infants with benign hypercalcæmia; in the preceding 2½ years I had seen none though I particularly looked out for it. I cannot explain this "hypercalcæmia-free" period. The clinical course in all 7 children was remarkably mild[1] and the serum-calcium did not reach the high levels found in many of the 33 cases I saw in Belfast between 1952 and 1955.[2] Assuming a normal serum-calcium range of 10–12 mg. per 100 ml., and making allowance for different methods of estimation,[3 4] the biochemical picture is as below.

Highest serum calcium found (mg. per 100 ml.)	*Belfast series (33 cases)*	*South Shields series (7 cases)*
12·1–13·0	12	6
13·1–15·0	12	1
15·1–19·8	9	0
	Range of highest values (mg. per 100 ml.)	
Belfast series	12·1–19·8	
South Shields series	12·2–13·6	

The pattern of infant feeding differed little in the 2 groups; the infants were fed almost exclusively on vitamin-D fortified dried milk, but vitamin-D supplements were given less often to the South Shields babies.

The clinical course of these few cases suggests that the severity of benign infantile hypercalcæmia has recently

1. Creery, R. D. G., Neill, D. W. *Lancet*, 1954, ii, 110.
2. Creery, R. D. G. Communication to Ulster Medical Society, 1956.
3. Trinder, P. Communication to Association of Clinical Biochemists, 1957.
4. Trinder, P. *Analyst*, 1960, **85**, 889.

diminished. As the disease is generally held to be related to excessive intake of vitamin D in susceptible infants, the sharp reduction in vitamin-D fortification of infant foods brought into force in 1957 [5] may well be responsible for this change. But the risk of hypercalcæmia developing in some infants is still present; is the present officially recommended figure of 400 I.U. vitamin D daily still too high ? Information on this, and on the prevalence of infantile hypercalcæmia in this country, should be forthcoming from the next report of the British Pædiatric Association's survey on hypercalcæmia and rickets.[6]

With the present level of vitamin-D supplementation of infant diets, we may have to accept the occasional mild case of infantile hypercalcæmia in order to protect the majority of babies from rickets. It is comforting that in general both the short-term [1] and long-term [7] prognosis for hypercalcæmic infants has been shown to be reasonably good.

I am grateful to Mr. J. F. Kirkland for his help with the biochemical estimations.

South Shields,
County Durham. R. D. G. CREERY.

POMP AND CIRCUMSTANCE

SIR,—I entirely agree with Professor Sanjivi (Feb. 4) and doubt your correctness in commending [8] the suggestion of the *Oxford Medical School Gazette* that all clinical teaching should take place in a room adjacent to the ward. Most of our general-ward patients do not understand English, the language in which medicine is still taught in our country, so we seldom have to restrict discussion in front of them. As a matter of fact, they are encouraged by the thought that something very important is being discussed by many young doctors for their benefit! We feel we should concentrate more on real bedside teaching with demonstration of physical findings, on which we have to depend for diagnosis in most of our non-teaching hospitals and village primary centres which cater for most of the Indian population.

Madurai,
South India. K. A. KALYANAM.

5. Ministry of Health Circular 89/57.
6. British Pædiatric Association. *Arch. Dis. Childh.* 1960, **35**, 415.
7. Mitchell, R. G. *ibid.* p. 383.
8. *Lancet*, 1960, ii, 1071.

Public Health

Infectious Diseases in England and Wales

Diseases	Week ended March			
	4	11	18	25*
Diphtheria	10	6	8	1
Dysentery	683	729	761	694
Encephalitis:				
Infective	4	1	1	2
Postinfectious	10	9	8	..
Food-poisoning	113	94	124	140
Measles excluding rubella	35,709	36,616	38,507	37,993
Meningococcal infection	23	24	24	22
Ophthalmia neonatorum	21	25	18	29
Paratyphoid fever	2	2	3	5
Pneumonia, primary or influenzal	657	512	390	302
Poliomyelitis:				
Paralytic	2	3	1	9
Non-paralytic	..	2	4	2
Puerperal pyrexia	170	180	180	148
Scarlet fever	523	515	553	521
Smallpox	..	..	..	..
Tuberculosis:				
Respiratory	465	376	426	414
Meninges and C.N.S.	5	3	2	6
Other	48	59	55	59
Typhoid fever	..	..	2	1
Whooping-cough	823	955	854	826

* Not including late returns.

Obituary

WILLIAM GEORGE SAVAGE

Kt, M.D., B.Sc. Lond., Hon. M.D. Brist., D.P.H.

As a county medical officer of health Sir William Savage was for many years responsible for the health of Somerset; but by his work for the safety of milk, food, and water he did much to safeguard and improve the health of the whole country. He died on April 6 at his home in Winchester at the age of 88.

He was born in Jamaica, but he came to this country to study, and after graduating B.SC. from University College London in 1894 he went on to take his medical degree two years later. In 1897 he took his D.P.H., and though he spent the next few years in house-appointments and academic posts, including a lectureship in bacteriology at University College, Cardiff, public health was already his interest if not his career. When in 1903 he accepted the post of medical officer of health for Colchester he was already a seasoned bacteriologist, and he soon began to publish the results of his investigations of such local phenomena as tidal mud and surface wells. Some of his earliest work on milk appeared in the report of the old Local Government Board in 1906–7 and the first edition of his book *Bacteriological Examination of Water Supplies* appeared in 1906.

After he moved to Somerset in 1909 to become the county's first M.O.H., despite his heavy administrative responsibilities he continued his bacteriological studies. He had already reported the isolation of what he called the Gaertner group of bacilli, and he continued this work on food-poisoning with the support of the Medical Research Council. It culminated in two reports, with Bruce White, on the serology of the salmonella group and their relation to food-poisoning. Linked with these investigations was Savage's interest in canned foods. In 1923 he chose " canned food in relation to health " as the title of his Milroy lectures to the Royal College of Physicians, which were later the basis of one of his lucid and instructive books; and in 1939 he deliberately chose the same title for his Chadwick lecture, which was cancelled by a war which unfortunately gave special topical interest to the subject.

His move to an agricultural county sharpened his interest in milk supplies and their protection against tuberculous and streptococcal infections. His early and firm advocacy of pasteurisation and the creation of tuberculosis-free herds, based on firsthand experience in farm, factory, and laboratory, was vigorously expressed in his Mitchell lecture to the Royal College of Physicians in 1933 and in his book on the *Prevention of Human Tuberculosis of Bovine Origin*.

Savage had so much relevant experience and showed so much sensible foresight in its application that many people and bodies turned to him for advice, and to this journal he was often a friendly and valued counsellor. He was a past president of the Society of Medical Officers of Health. He was an examiner for the universities of London, Reading, Wales, and Bristol.

He retired in 1937, and in the following year he was created a knight and received the honorary degree of M.D. from the University of Bristol. To begin with, his retirement was purely nominal, and in a letter to a friend he gave the following programme for the first weeks of his new leisure:

Worked in my big garden; took chair at People's League of Health meeting on milk policy; investigated a food-poisoning

outbreak; wrote an article for a health propaganda campaign; gave evidence for a local authority in a housing appeal case; visited a research canning station and discussed canning problems with the director; wrote summaries for the Bureau of Hygiene.

Soon after the war he undertook his last major official task when in 1948 he became chairman of the Ministry of Food's working party on the catering trade. He took an active part in preparations for the National Health Service, and he was a member of the team which surveyed the hospital service of East Anglia. New editions of his books continued to appear, and in 1952 *The Making of Our Towns*, a history of the growth of towns in Britain, was published. Of these later years A. D. relates:

"Savage spent his retirement in Winchester and found solace in his hobbies—archæology and gardening. Almost the last time he was seen at a public health gathering was about 5 years ago at the Bournemouth congress of the Royal Society of Health when he attended the Mayor's reception and everyone marvelled at his mental and physical vigour. Probably very few remember him in the hey-day of his outstanding career. Though his outlook was up to date and he took an active part in the development of the personal health services, he never allowed anyone to forget that control of the environmental services must always remain an essential part of the duties of a health officer."

J. L. B. writes:

"We all loved Sir William—his splendid vitality, his mental vigour, his clarity of mind and purpose. In his book *Practical Public Health Problems*, we see the essence of his life-work in preventive medicine rather than therapeutics. His driving purpose was to track down disease to its source, and among his outstanding contributions was the work that he did in establishing the pasteurisation of milk in its daily use in the home. He is remembered too for his work in defining salmonella of food-poisoning. To his wide basic knowledge he added an expert's view of geology which enabled him to give authoritative advice on problems of water supply. Outside his professional duties he was known as a historian with astonishingly wide knowledge of the ancient world and of the middle ages, which made him a valuable president of the Somerset Archæological Society."

Sir William leaves a daughter and a son, Dr. S. W. Savage, who is M.O.H. for Warwickshire.

ROBERT AIM LENNIE

M.D., LL.D. Glasg., F.R.F.P.S., F.R.C.O.G.

Dr. R. A. Lennie, whose death on March 26 we announced last week, was regius professor of midwifery in the University of Glasgow for seven years. For many more he served the Royal Maternity Hospital and the Victoria Infirmary as a clinician and a teacher, and, as one of his colleagues once said, "some of the most important lessons he taught his students derived from a natural display of professional efficiency and ethical standards of the highest order".

He was born in 1889, the fifth son of Ritchie Lennie of Cambuslang. He was educated at Glasgow High School and University from which he qualified in 1912. He held a house-appointment at the Royal Maternity and Women's Hospital before the 1914–18 war, during which he served with the R.A.M.C. in Gallipoli, Egypt, Palestine, and France. On demobilisation he returned to his post at the hospital, and in 1920 he was appointed assistant visiting obstetrician there, and assistant gynæcologist to the Victoria Infirmary. For many years his obstetric practice centred on the Infirmary. He also became chief obstetric surgeon to the Royal Maternity and Women's Hospital, lecturer in midwifery at the university, and professor of midwifery and gynæcology at St. Mungo's College.

During the late war his work was again interrupted. As an experienced Territorial officer he was appointed colonel in charge of the 600-bed military hospital at Drymen. But after serving in this position for two years he was recalled to civilian duties at the request of the Department of Health for Scotland. In addition to his usual duties he was then asked to take charge of the gynæcological department of the Emergency Medical Services hospital at Bangour.

Soon after the war in 1946 he was appointed to the regius chair, and two years later he also took over the gynæcological department at the Western Infirmary. He retired in 1954, and the following year Glasgow University conferred on him the honorary degree of LL.D.

He was a founder member of the Royal College of Obstetricians and Gynæcologists and sat on the first council. He was elected to the fellowship in 1936. He was also a chairman of the Central Midwives Board for Scotland and a commandant of the St. Andrew's Ambulance Corps.

H. R. MacL. writes:

"While the Glasgow School has always been renowned for its academic achievement, Robert Lennie's personal qualities brought to it a harmony which had for some time been lacking, for he was a kindly modest man, with a great gift of humour. The gross obstetric abnormalities which were met in hospital in the early days of his career gave ample scope for study and he contributed to textbooks and wrote articles for scientific journals; so many, in fact, that on one occasion he was heard to say 'I stopped writing as I was in danger of becoming the Edgar Wallace of Obstetrics.' He was in his time president of many medical societies. One of his greatest sources of pleasure, however, was his membership of the Gynæcological Club of Great Britain, where his gift of good-fellowship gained him both popularity and respect.

"Apart from his professional and military interests, Robert Lennie was a great sportsman. A keen golfer, he became president of the Glasgow Golf Club and won the Munro Kerr trophy, which had been presented to the club by a distinguished predecessor—a coincidence which gave him great pleasure. As a Scotsman he loved his country; he shot on its moors and fished on its rivers. He and his wife, who is herself a doctor, kept an 'open house' to all who were associated with him in his many and varied activities. His was a full and well-rounded life."

Professor Lennie married in 1926 Dr. Mary Jeffrey, who survives him.

JAMES MACLURE SMELLIE

O.B.E., T.D., M.D. Edin., M.D. Birm., F.R.C.P.

Dr. J. M. Smellie, emeritus professor of pædiatrics in the University of Birmingham, died at his home at Tanworth-in-Arden, Warwickshire, on April 3, at the age of 67.

He was the son of Alderman James Smellie, a former mayor of Dudley, Worcestershire. He was educated at Dumfries Academy and Edinburgh University, for which he played hockey. Soon after qualifying in 1916 he joined the R.A.M.C., and he served for over three years in Macedonia. On demobilisation in 1920 he was appointed resident medical officer to the Birmingham General Hospital. He spent the next two years in London while holding a house-appointment at The Hospital for Sick Children, Great Ormond Street. In 1922 he returned to Birmingham to take up the post of medical registrar and pathologist to Queen's Hospital, and soon afterwards he was appointed physician to outpatients at the Children's Hospital. Two years later he was also elected to the staff of the Birmingham General Hospital. He was medical tutor to the University of Birmingham from 1924 to 1934 and a lecturer in pharmacology and therapeutics and in diseases of children to the university for over twenty years. He was elected F.R.C.P. in 1932. In 1939 his Ingleby lecture on infantile diarrhœa was based on a study of 500 cases.

As a Territorial officer he was mobilised in the R.A.M.C. in 1939, and he served in France, India, Burma, and Assam. From 1944 to 1945 he was consulting physician to the Eastern Command, India, with the rank of brigadier. He was appointed O.B.E. in 1944. On his return to civilian practice in 1947 he succeeded the late Sir Leonard Parsons as professor of pædiatrics in the University of Birmingham, and he was the first full-time holder of the chair. He was a past president of the Pædiatric Section of the Royal Society of Medicine and of the British Pædiatric Association. He was an examiner in medicine to the Universities of Birmingham and London, and in pædiatrics to the University of Manchester. He retired in 1958.

A. G. W. W. writes:

"Professor Smellie was the essence of modesty, and he was the kindest, gentlest, and most friendly person whose only thought in life seemed to be to help others to the utmost of his ability. He was an extremely good physician and pædiatrician, and before he became professor of pædiatrics he had a large private practice. His contributions to the literature were numerous, and while he held the chair of pædiatrics a large amount of valuable research was done at the Children's Hospital under his guidance. When he retired a little over two years ago he seemed full of health and vigour, and all his many friends were filled with regret at his departure when he still seemed to have so much to offer to the hospitals and university he had served so well. Almost immediately illness befell him. He surmounted successive disasters with the courage and determination that were an essential part of the man, and it was still hoped that he would enjoy many years of happy retirement and continue to carry out the duties which the university, the teaching hospital, and the regional hospital board asked him to undertake. His death came suddenly after a quiet country walk with his wife."

Professor Smellie married in 1929 Kathleen Lamsdale, who survives him with two sons.

IVAN HENRY McCAW

M.D. Belf.

Dr. Ivan McCaw, physician in charge of the dermatological department of the Royal Victoria Hospital, Belfast, died on March 17 at the age of 64.

The son of Dr. John McCaw, one of the earliest specialists in diseases of children in Belfast, he was educated at the Royal Belfast Academical Institution. In 1914 he entered the Queen's University of Belfast as a medical student, but in 1915 he was commissioned in the Royal Irish Rifles and in 1917 he was badly wounded at the battle of Messines. Later he resumed his medical course, graduating in 1922 with honours. After holding resident appointments at the Royal Victoria Hospital, Belfast, he decided to specialise in dermatology, and he spent some years in postgraduate studies, first in Edinburgh, then for a short time in Vienna, and finally as a clinical assistant to the late Dr. H. W. Barber at Guy's Hospital. On returning to Belfast McCaw was appointed physician to new departments of dermatology at the Royal Victoria Hospital and at the Royal Belfast Hospital for Sick Children, which were the first posts of the kind to be created in Northern Ireland.

G. B. D. writes:

"McCaw did not regard himself as a leading dermatologist or as important in any other way, but despite his humility he was in the highest rank of British dermatologists and he served as president of the British Association of Dermatology in 1948. His great achievement, however, was in building a dermatological service for the whole of Ulster. He could do this partly because he had the necessary vision and organising ability, but above all because he was a leader who readily won the absolute trust of all those who worked with him as well as their affection. Everyone in Northern Ireland knew him, whether in or outside the medical profession, and his election at different times as president of the Queen's University Services' Club and as captain of the world-famous Royal County Down Golf Club, reflects the high esteem in which he was held by his fellow Ulstermen.

"He was a magnificent character, gentle, warm-hearted, totally unselfish, full of indigenous humour and apparently never out of humour. If he ever thought badly of anyone, he certainly never said so. Though he died rather young, he lived to see the fruits of his professional labours, a highly efficient and closely welded dermatological service for Ulster."

Dr. McCaw is survived by his widow, a son, and a daughter.

PETER SIDNEY DAVIS

M.B. Cantab., M.R.C.P.

Dr. Peter Davis, senior registrar in general medicine and rheumatology at the West London Hospital died on March 30 at the age of 38.

He was educated at Oundle, St. John's College, Cambridge, and the Westminster Hospital. He showed outstanding promise at school and college, and as a medical student won many prizes. After a house-appointment and registrarship at the Westminster he worked for a time in the neurological department of St. George's Hospital before moving to the West London Hospital six years ago. There he became interested in the problems of the rheumatic diseases, particularly those raised by the long-term treatment of severe cases of rheumatoid arthritis with corticosteroids. He was one of the first to show that wounds heal normally in patients on reasonable doses of corticosteroids and he worked out a meticulous regime of extra steroid coverage for patients who had to have operations. He was an enthusiastic territorial and a medical specialist in one of the T.A. London hospitals.

O. S. writes:

"Peter was a gay and delightful colleague. It was a particular joy and a great stimulus to me to discuss research problems with him, for I could then appreciate his wide knowledge of general medicine and physiology and his critical scientific approach. At the same time he was intensely human and beloved by his patients who knew that he was prepared to go to any amount of trouble on their behalf. He was also extremely popular among students at the West London, for he was an excellent clinical tutor and they recognised his ability to help them through exams. He had taken a major part in the clinical research of the rheumatism department and he was in the forefront of the younger group of rheumatologists."

W. S. C. C. sends the following personal tribute:

"Peter Davis was a tall quiet man of somewhat diffident manner, with a first-class brain, who inspired admiration and affection in everyone with whom he came into more than casual contact. He faced his unexpected tragic illness with resignation and calm courage. He will be much missed."

Dr. Davis leaves a wife and two young sons.

CHARLES HARDIMAN LAVER

M.A., B.M. Oxon., F.R.C.S.E.

Mr. C. H. Laver, who until his retirement was a consultant surgeon to the Redhill hospital group, died on Feb. 11 at the age of 68.

He was born in South Africa, but he went to school in Bedford, and in 1910 to Guy's Hospital. He saw active service in 1914 at the first battle of Ypres and was commissioned in the R.F.A. in 1915. He returned to Guy's in 1917 to qualify and then served as a surgeon in the Navy. After the war he went to Oxford as a demonstrator in anatomy, and took the B.M. degree and the F.R.C.S.E. In 1922 he went into general practice in Redhill. He was appointed to the East Surrey Hospital

as assistant surgeon two years later and as surgeon in 1930. He gave up his general practice in 1948 on being appointed consultant surgeon to the Redhill hospital group. After he retired in 1958 he settled in Bournemouth. L. J. B. writes: "Charles Laver had many interests including astronomy. He won an international bronze skating medal in 1933, and he played water polo for Oxford and Guy's. He did everything with great enthusiasm, vigour, and humour. His generosity, kindliness, and optimism will be missed by his many patients, colleagues, and friends."

SINCLAIR HOWARD ARMSTRONG

M.D. Harvard

Dr. S. Howard Armstrong, Jr., director of biological sciences and medical education at Cook County Hospital and professor of medicine in the University of Illinois, who died recently at the age of 48, combined a deep knowledge of mathematics and biophysics with outstanding qualities as a physician.

He graduated from Princeton in 1933 and from Harvard Medical School in 1937. His qualities and his interest in philosophy as well as medicine were recognised at both universities; and soon after he received his medical degree he was offered both an appointment in the department of philosophy at Princeton and election to the Society of Junior Fellows at Harvard. He chose the fellowship and during his three years at Harvard he worked with Edwin Cohn and J. L. Oncley on the separation, identification, and chemistry of plasma-proteins, on which he became an authority. In 1948 he was appointed chairman of the department of medicine at Presbyterian Hospital in Chicago and professor of medicine at the University of Illinois. He soon developed a keen interest in medical education, and during the past eight years he has been director of medical education at Cook County Hospital, Chicago, a large teaching institution with 3800 beds. He also served on the editorial board of several medical journals, on committees of scientific societies, and as a consultant to the United States Government.

R. M. K. writes:

"During his early training at Boston City Hospital, Armstrong came under the influence of the late Soma Weiss, Hersey professor of physic at Harvard. From this contact grew his special feeling for work in a large city hospital, and he was adept at persuading the city fathers in Chicago to take an active interest in their hospital and its standards. Working through them, he accomplished his aims in improving medical care, education, and research at the Cook County Hospital. His young men and residents were devoted to him, and medical students were stimulated by his eccentric and unique methods of drawing the best out of them. He was a talented pianist, and carpentry and yachting were his hobbies. He enjoyed experimentation in these activities, as he did in medicine. His large yacht—one of the few with a welded steel hull—was built in the garage on Saturday afternoons with his friends, his residents, and his students—all of whom willingly accepted his leadership in the boatyards as they did on the wards."

Appointments

ARKLE, D. J., B.M. Oxon., D.P.M.: medical director, Fair Mile Hospital, Wallingford.

CLARE, D. E., M.B. Durh., D.P.H.: M.O.H. for Wells, Shepton Mallet, and Street.

FALCONER, G. M., M.B. Edin., D.A.: anæsthetist (S.H.M.O.), Victoria Hospital and hospitals in Cupar and St. Andrews.

POLLITT, W. A., M.R.C.S., D.P.H.: senior assistant divisional M.O., Lancashire (division No. 9).

Manchester Regional Hospital Board:

GORDON, THOMAS, M.B. Belf., D.PATH.: assistant pathologist, Salford Royal Hospital.

GRAYBURN, R. W., M.B. Durh., M.R.C.O.G., D.OBST.: consultant obstetrician and gynæcologist, Lancaster and Kendal hospital group.

MCHUGH, J. H., M.B. N.U.I.: assistant psychiatrist, Calderstones Hospital.

MCINTYRE, HUGH, L.R.C.P.E., D.A.: part-time assistant anæsthetist, Preston and Chorley hospital group.

ZABRON, W. W., MED. DIP. Warsaw, M.R.C.S.: senior casualty officer, Rochdale and district hospital group.

Notes and News

THE WELLCOME TRUST

THIS year the Wellcome Trust celebrates its silver jubilee. Since it came into full operation about five years ago, it has distributed no less than £3 million in grants.

In making awards the trustees have aimed at complementing the activities of other grant-making bodies and filling gaps in the provision for medical research, more particularly in pharmacology and pharmacy, veterinary medicine, tropical medicine, the history of medicine, experimental physiology, biochemistry, and biophysics. The absence of geographical limitations has enabled grants to be made to many centres overseas; and the third report of the Trust (1958–60) [1] records two in the U.S.A.—for a research laboratory at Johns Hopkins Hospital, Baltimore, and to establish a Henry S. Wellcome professor for ten years at the Massachusetts General Hospital, Boston. Research fellowships and Wellcome research travel grants have been awarded to workers from the Commonwealth and from foreign countries as well as to those from the United Kingdom.

In 1958–60 £57,436 was awarded for research fellowships, scholarships, and personal grants to young workers in training; £40,725 was given for research expenses; 269 Wellcome research travel grants were awarded at a cost of £53,000; £8350 was provided for travelling expenses of British participants at international congresses on medical research; and £6420 was given to the organisers of small symposia on particular aspects of research. Ten travelling research fellowships were awarded to enable established research workers to gain further experience overseas (£17,300); a further £60,000 was given to the Medical Research Council to provide five Sir Henry Wellcome travelling fellowships annually for five years; and £4320 was awarded in aid of publications, including guarantees to cover the *Journal of Embryology and Experimental Morphology* and the *Journal of Reproduction and Fertility*.

The report pays a warm tribute to Sir Henry Dale, who retired from the chairmanship of the Trust on reaching the age of 85. He was one of the original five trustees named in Sir Henry Wellcome's will, and had been chairman for twenty-two years. Lord Piercy has now been chairman for a year; and Sir Henry Dale is scientific consultant to the Trust.

PROPRIETARY PREPARATIONS

A VERY high proportion of proprietary preparations classified by the Cohen Committee fall into category S. This comprises:

1. Preparations whose active therapeutic constituents are identical with those of preparations described in the *British Pharmacopœia, British Pharmaceutical Codex*, and *British National Formulary*. (These may or may not have exact unbranded equivalents.)
2. Preparations whose active therapeutic constituents are modifications of those preparations described in the *B.P.*, *B.P.C.*, or *B.N.F.* (There are rarely any exact unbranded equivalents of these.)
3. Mixtures of drugs in category N ("new drugs of proved value which are not yet 'standard'") with drugs in (1) or (2).
4. Elegant preparations of drugs in category N.

In a report [2] circulated this week to doctors in the National Health Service, the committee say that they are drawing up a list of preparations in the *B.P.*, *B.P.C.*, and *B.N.F.* which are available in unbranded form and whose active therapeutic constituents are identical, quantitatively and qualitatively, with those of proprietary preparations in paragraph no. 1 above.

They go on to say that category S contains many admixtures whose undiscriminating prescription could be questioned on therapeutic grounds because:

(*a*) They are combinations of drugs of similar action (e.g., of

1. Obtainable from the Trust at 52, Queen Anne Street, London, W.1.
2. Standing Joint Committee on Classification of Proprietary Preparations: Report on Classification in Category S. 1961. H.M. Stationery Office. Pp. 6. 6*d*.

analgesics or hypnotics) which give no therapeutic advantage over standard single drugs in adequate dosage; or

(*b*) they include a fixed proportion of a drug to counter the untoward side-effects of the main therapeutic agent, whereas good treatment demands that the quantity of the corrective should be determined by the need, which varies with each patient (examples are an opiate and aperient, or phenobarbitone and bemegride); or

(*c*) they combine in a fixed proportion drugs of differing and valuable therapeutic action, whereas the relative amounts should be determined by the individual patient's needs (an example is aspirin mixed with corticosteroids); or

(*d*) they include a preparation which is not regarded as therapeutically superior to standard preparations.

Though there should be no absolute restriction on the prescribing of any drug that the general practitioner thinks necessary for his patient, the committee believe that he "need not normally go outside the drugs and preparations described in the *B.P.*, *B.P.C.*, and *B.N.F.* together with drugs in categories N and P" (the latter being preparations on which judgment is suspended). "Before he decides to prescribe any other preparation he should satisfy himself that the one chosen is better for his particular patient and that it is the only reasonable choice to make, as he may be called upon to justify his action if the cost of his prescribing is being formally investigated."

The report was presented to the Health Ministers with reservations by two members of the committee (Mr. J. C. Hanbury and Mr. D. E. Sparshott) who think that the above recommendation, if carried to its logical conclusion, will mean the virtual elimination of the prescribing of preparations coming within the present category S. The strength and prosperity of the British Pharmaceutical Industry, they say, depends on the sale of branded goods of quality, and if most of these products were no longer prescribed in the N.H.S. the industry would be crippled, and its ability to conduct research would be seriously diminished. "In a few years' time this country would become largely dependent for new advances upon the pharmaceutical industries of the United States and the Continent of Europe."

FUTURE OF MENTAL HOSPITALS

THE Minister of Health has asked regional hospital boards to review the mental hospital accommodation in their areas, not only in preparation for a realistic programme of hospital building but to ensure that "no more money than is necessary for short-term use is spent on the up-grading or reconditioning of mental hospitals which in ten or fifteen years time are not going to be required". Where parts of conveniently sited mental hospitals could be adapted for short-stay patients and for the rehabilitation of longer-stay patients, it would probably be as economical—and no less effective—to modernise as to build new units. But for the large, isolated, and unsatisfactory building, closure would nearly always be the right answer. Estimates of future bed requirements could not be exact predictions, but the Minister expected that the number of beds needed for mental patients might be halved in the next sixteen years. He emphasised, however, that this did not mean a reduction in psychiatric services—rather the reverse. A similar number of beds, more intensively served, and with appropriate outpatient and day-hospital provision, would deal more effectively with the patients needing hospital treatment.

NORTH STAFFORDSHIRE MEDICAL INSTITUTE

THE North Staffordshire Medical Society is appealing for £100,000 to build a medical institute in Stoke-on-Trent. North Staffordshire is a geographically isolated industrial area with a population of 500,000 and is roughly equidistant from Birmingham, Liverpool, and Manchester. Since the National Health Service began, there has been a rapid expansion in the hospital services, and the two major hospitals, which are within a quarter of a mile of one another, now have over 1300 "acute" beds and a staff of 75 consultants. These hospitals will shortly be linked by a new common outpatients' department to be built centrally between them, and the Birmingham Regional Hospital Board are planning the development of a fully comprehensive hospital centre at a cost of £10 million. Clearly, therefore, the area has the opportunity of becoming an important medical centre. On the other hand good medical practice largely depends on the academic side of professional life—for which there are at present few facilities in North Staffordshire. The new medical institute is to have a first-rate lecture theatre, a lending library, and a pathological museum. The regional hospital board have offered a site for the building midway between the two hospitals; but the money will have to come from private sources. The building will be the focus of academic activities in the district. Most of the four hundred general practitioners in the area are members of the society, and the institute will therefore be a place where doctors working in the hospitals will meet those working outside.

It is also intended that the institute shall foster research. The isolated and relatively static population of the district is particularly suitable for long-term clinical studies. As a start, people with research projects will be given rooms in the building where they may keep their documents or case-records and be provided with secretarial help. If funds permit, more ambitious research projects may be possible.

Both the local medical men and the public have already responded in a very encouraging way, and it is hoped that building will start next year.

NEW BIOLOGY JOURNAL

MANY workers in biology have difficulty in finding a medium for theoretical papers. The problem should be solved, at least partly, by the *Journal of Theoretical Biology*,[1] the policy of whose editorial board is to accept only papers on theoretical aspects. The scope of the journal is broad—the first issue includes papers on biochemistry, animal ecology, and the application of the quantum theory to empirical biology. Several of the articles have immediate practical applications.

A fairly rigorous mathematical treatment of permeation through a spherical membrane by Hall [2] leads to some important conclusions about hæmolysing erythrocytes. A paper by Andrewartha and Browning [3] on resources in animal ecology has special pertinence at a time when the world population threatens to outgrow the supply of food. Their discussion is based on the relation between host and parasite, and between the dietary and breeding habits of an animal population and its sources of food. The conclusions drawn about the influence of these factors on the size of the population—whether it will increase, decrease, or die out—could undoubtedly be extended to man. Williams [4] puts forward some fascinating speculations to account for the complexity and apparently unnecessary lengths of the chains of catalysts involved in biochemical systems.

JOURNAL OF ATHEROSCLEROSIS RESEARCH

ACCOUNTS of research into atherosclerosis are spread over a large number of journals; and the object of the *Journal of Atherosclerosis Research*,[5] of which the first issue has appeared, is to provide an international medium to keep workers acquainted with advances in this complex and rapidly expanding subject. The emphasis will be on fundamental research, but review articles and surveys of recent reports will also be included.

The first issue, which has set a high standard, opens with a comprehensive review by T. Crawford of morphological aspects of the pathogenesis of atherosclerosis. Original articles include one by C. J. F. Böttcher and C. M. van Gent on changes in the composition of phospholipids and of phospholipid fatty acids associated with atherosclerosis in the human aortic wall; one by W. Schrade and his colleagues on the fatty-acid distribution in the lipid fractions of healthy persons of different ages, patients with atherosclerosis, and patients with idiopathic "hyperlipidæmia"; and one by S. Gerö and his colleagues on the role of intimal mucoid substances in pathogenesis. H. M. Sinclair reports the principal contributions to the Milan

1. *Journal of Theoretical Biology*. Chief editor: J. F. Danielli. London: Academic Press. Vol. 1, no. 1, January, 1961. Annual subscription 121*s*. 6*d*.; private subscription 86*s*.
2. Hall, C. G. *ibid*. 1961, **1**, 198.
3. Andrewartha, H. G., Browning, T. O. *ibid*. p. 83.
4. Williams, R. J. P. *ibid*. p. 1.
5. *Journal of Atherosclerosis Research*. To be published six times a year. Manuscripts should be sent to the editorial secretary, Dr. F. P. Woodford, Witte Singel 36, Leiden, The Netherlands. Subscriptions (£6 5*s*. or $17.50) should be sent to Elsevier Publishing Company, 110 Spuistraat, Amsterdam-C, The Netherlands.

symposium of June, 1960, concerning drugs affecting lipid metabolism.

The contents are prefaced by summaries of each article in English, French, and German. This excellent feature might be expanded to include a summary in Russian: in recent years there has been free exchange of ideas between many investigators in Western Europe, Scandinavia, and the United States; but one of their main handicaps is comparative ignorance of investigations in Eastern Europe and Russia. Any journal which could provide a forum and translation service for Russian work would be most welcome; and, since the editorial board includes representatives from Moscow, Warsaw, Budapest, and Prague, the new journal might be in a position to make this contribution.

University of Cambridge

On March 25 the following degrees were conferred:

M.D.—J. K. F. Mason.
M.Chir.—W. M. Keynes,* Henry Sunderland, K. L. Williams.
M.B.—I. Fraser Brockington, R. J. Heald, J. S. Kirkham, M. J. Leverton, L. P. Martin, H. R. Patterson, A. J. Whitworth.

* By proxy.

University of Toronto

Dr. John D. Hamilton, professor of pathology, has been appointed dean of the faculty of medicine in succession to Dr. J. A. MacFarlane.

Institute of Diseases of the Chest, London

Clinical demonstrations for doctors will be arranged by Mr. N. C. Oswald at the Institute, in the grounds of the Brompton Hospital, Fulham Road, S.W.3., on Fridays, at 5 P.M. from April 28 to July 7.

Society of Apothecaries of London

Faculty of the History of Medicine and Pharmacy.—The annual general meeting of the faculty is to be held on Friday, April 28, at 4.30 P.M., at Apothecaries' Hall, Blackfriars Lane, E.C.4. At 5 P.M. Sir Geoffrey Keynes will give a Gideon de Laune lecture. His subject will be Timothy Bright.

College of General Practitioners

South-West England Faculty.—On May 6, at Torquay, Devon, this faculty is to hold a symposium on emotional disorders in general practice. Further particulars may be had from Dr. W. H. Hylton, Eglinton, Princes Road, Clevedon, Somerset.

International Conference on Mental Retardation

This conference is to be held from Aug. 14 to 19 in Vienna. Further particulars may be had from the secretariat of the conference, Universitäts-Kinderklinik, Lazarettgasse 14, Vienna IX.

International Congress of Pædiatrics

This congress will be held from Sept. 9 to 15, 1962, in Lisbon. Further particulars may be had from the secretariat of the congress, Clínica Pediátrica Universitária, Hospital Santa Maria, Avenida 28 de Maio, Lisbon, 4, Portugal.

International Congress of Plastic Surgery

This congress will be held from Oct. 13 to 18, 1963, in Washington, D.C. Further particulars may be had from Dr. Leslie H. Backus, 217, Linwood Avenue, Buffalo 9, New York.

Central Midwives Board

Mr. Arnold Walker has been re-elected chairman and Prof. A. A. Moncrieff, deputy chairman of the board.

Perinatal Mortality Survey

On April 28, at 5 P.M., at a meeting of the Section of Pædiatrics of the Royal Society of Medicine, at 1, Wimpole Street, London, W.1, the first results of this survey, held under the auspices of the National Birthday Trust Fund, will be presented. The meeting will include reports on respiratory-distress syndromes, principal post-mortem lesions, breech deliveries, cæsarean sections, and intrapartum asphyxia.

Prevention of Thromboembolism in Surgery

A conference on this subject is to be held on Saturday, May 27, at the Dijkzigt Hospital, Rotterdam, Holland. Speakers from this country will include Dr. D. G. Chalmers and Dr. Simon Sevitt. Further particulars may be had from Dr. J. M. Greep, Surgical Department, Dijkzigt Hospital, Rotterdam, 2.

Prof. C. F. W. Illingworth has been appointed an honorary surgeon to the Queen in Scotland in succession to Mr. G. G. Bruce, who becomes an extra surgeon to her Majesty in Scotland.

Prince Bertil of Sweden has personally appointed Mr. C. Naunton Morgan as commander of the Order of the Pole Star, and Dr. E. M. Herbert, Dr. J. D. Ebsworth, and Mr. S. M. Cohen as knights of the order.

Mr. R. F. Guymer has been appointed a member of the World Health Organisation's advisory committee on the joint medical services.

The distinguished service award of the American Hospital Association has this year been made to Dr. E. M. Bluestone, director of the Montefiore Hospital, New York City, from 1928 to 1951.

A series of lectures and clinicopathological meetings are being held at the Brook General Hospital, Shooters Hill, London, S.E.18, and Lewisham General Hospital, S.E.13, on Wednesdays at 5.45 P.M., from April to July. On April 19, at the Brook General Hospital, Dr. E. J. Moran Campbell will speak on breathing and breathlessness.

A meeting of the Manchester Royal Infirmary Old Residents' Club will be held at the Midland Hotel, Manchester, on Saturday, Oct. 7.

The spring dinner of the Wessex Rahere Club will be held on Saturday, May 13, at the Royal Clarence Hotel, Exeter. The secretary of the club is Mr. A. Daunt Bateman, 11, The Circus, Bath.

Diary of the Week

APRIL 16 TO 22

Sunday, 16th

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1.
10.15 A.M. Mr. W. D. Doey: Common Ear, Nose, and Throat Conditions.

Monday, 17th

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE, 28, Portland Place, W.1
3.30 P.M. Dr. A. G. Cross: Common Eye Defects and Ailments.

Tuesday, 18th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
4.15 P.M. Dr. A. A. Barton: Replication of Species. (Arnott demonstration.)

WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY, 91, Dean Street, W.1
5.30 P.M. Mr. K. I. Nissen: Orthopædic Aspects of Neurological Conditions.

SOCIETY FOR THE STUDY OF ADDICTION
8 P.M. (11, Chandos Street, W.1.) Sir Russell Brain: Report of the Interdepartmental Committee on Drug Addiction.

Wednesday, 19th

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
5 P.M. *Comparative Medicine.* Prof. F. W. Rogers Brambell, Dr. D. R. Bangham, Dr. A. E. Pierce: Transmission of Antibodies from Mother to Fœtus.
8.15 P.M. *General Practice.* Dr. R. N. R. Grant, Mr. Alexander Law, Mr. J. H. Hanby: Sore Feet.

ROYAL FREE HOSPITAL, Gray's Inn Road, W.C.1
5.15 P.M. Dr. Lillian Recant (St. Louis): Concepts of Nephrosis.

HARVEIAN SOCIETY OF LONDON
8.15 P.M. (11, Chandos Street, W.1.) Dr. A. E. Read: Iatrogenic Disease. (Buckston Browne prize essay.)

Thursday, 20th

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 P.M. Mr. D. P. Choyce: Development and Uses of All-acrylic Anterior Chamber Implants in Ophthalmic Surgery.

BRITISH ASSOCIATION OF PHYSICAL MEDICINE
10.30 A.M. (Westminster Medical School, S.W.1.) Opening of three-day meeting.

MANCHESTER MEDICAL SOCIETY
8. P.M. *Anæsthetics.* (Joint meeting with the Liverpool Society of Anæsthetists at Liverpool Medical Institution.) Dr. Mark Swerdlow: New Intravenous Anæsthetic. Dr. A. L. Stead: Dental Anæsthesia for Children.

Friday, 21st

ROYAL SOCIETY OF MEDICINE
5.30 P.M. *Epidemiology and Preventive Medicine.* Dr. J. A. Fraser Roberts: Genetics and the Public Health. (Presidential address.)

INSTITUTE OF LARYNGOLOGY AND OTOLOGY
3.30 P.M. Mr. S. E. Birdsall: Emergencies in Throat, Nose, and Ear Practice.